

# GLOBAL EPIDEMIOLOGY OF INFLUENZA: Past and Present\*

---

N. J. Cox and K. Subbarao

*Influenza Branch, Division of Viral and Rickettsial Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia 30333; e-mail: njc1@cdc.gov*

**Key Words** influenza, epidemiology, pandemic, mortality, pathogenicity

■ **Abstract** Pandemics are the most dramatic presentation of influenza. Three have occurred in the twentieth century: the 1918 H1N1 pandemic, the 1957 H2N2 pandemic, and the 1968 H3N2 pandemic. The tools of molecular epidemiology have been applied in an attempt to determine the origin of pandemic viruses and to understand what made them such successful pathogens. An excellent example of this avenue of research is the recent phylogenetic analysis of genes of the virus that caused the devastating 1918 pandemic. This analysis has been used to identify evolutionarily related influenza virus genes as a clue to the source of the pandemic of 1918. Molecular methods have been used to investigate the avian H5N1 and H9N2 influenza viruses that recently infected humans in Hong Kong. Antigenic, genetic, and epidemiologic analyses have also furthered our understanding of interpandemic influenza. Although many questions remain, advances of the past two decades have demonstrated that several widely held concepts concerning the global epidemiology of influenza were false.

## VIROLOGY AND THE MUTABILITY OF INFLUENZA VIRUSES

Influenza viruses are enveloped viruses of the family Orthomyxoviridae that contain a segmented RNA genome. Of the three types of influenza viruses, A, B, and C, the first two are associated with significant seasonal morbidity and mortality. Influenza A and B viruses were first isolated in 1933 and 1940, respectively (1, 2). Influenza A viruses can be subtyped according to the antigenic and genetic nature of their surface glycoproteins; 15 hemagglutinin (HA) and 9 neuraminidase (NA) subtypes have been identified to date. Viruses bearing all known HA and NA subtypes have been isolated from avian hosts, but only viruses of the H1N1, H2N2, and H3N2 subtypes have been associated with widespread epidemics in humans. Influenza A viruses of particular subtypes have also been isolated from

---

\*The US government has the right to retain a nonexclusive, royalty-free license in and to any copyright covering this paper.

a variety of animal species, such as H1N1 viruses from swine and H3N8 from horses. Different subtypes have not been identified among influenza B viruses.

The long-term epidemiologic success of influenza viruses is primarily due to antigenic variation that takes place in the two surface glycoproteins of the virus, the HA and NA. Antigenic variation renders an individual susceptible to new strains despite previous infection by influenza viruses or previous vaccination. Variation in influenza A and B viruses is caused by the accumulation of point mutations in the HA and NA genes (antigenic drift). During antigenic drift, a variety of mutations including substitutions, deletions, and insertions produce genetic variation in influenza viruses. These mutations occur because a viral RNA polymerase that lacks proofreading activity transcribes the influenza genome. Thus, nondeleterious errors that occur during genome replication may be preserved and subsequently amplified if conditions favor their survival. It appears that these genetic changes often encode amino acid changes in the surface proteins that permit the virus to escape neutralization by antibody generated to previous strains. Recent statistical analyses of HA sequence data have provided convincing evidence that positive Darwinian selection operates on antigenic sites in the HA (3, 4).

A second type of variation, antigenic shift, occurs only among influenza A viruses and describes a major antigenic change whereby a virus with a new HA (with or without other accompanying gene segments such as a new NA) is introduced into the human population. Antigenic shift occurs in at least two ways. It may occur when an animal or avian influenza A virus is transmitted without reassortment from an animal reservoir to humans or when a progeny virus with a new HA (with or without a new NA) arises as a result of genetic reassortment between animal and human influenza A viruses.

## THE ECOLOGY OF INFLUENZA A VIRUSES

Avian species, specifically shorebirds and waterfowl, are a reservoir of influenza A viruses of different subtypes in nature (reviewed in 5). With a few notable exceptions, influenza infections in these hosts are asymptomatic and are limited to the gastrointestinal and/or the respiratory tract (5). Influenza viruses infecting these hosts appear to be in evolutionary stasis compared with those infecting humans (6). High titers of influenza viruses are excreted from the gastrointestinal tract of infected birds, and viruses excreted into bodies of water can survive for several weeks (7). There is a recurring supply of susceptible birds each season and up to 30% of juvenile birds are infected (8). The viruses spread to other susceptible avian species, such as turkeys, presumably through contamination of water in the farms along the flyways of migratory bird populations (9, 10). Viruses that are apathogenic for shorebirds or waterfowl can be pathogenic for certain other avian species. For example, influenza A H5N1 viruses isolated from humans and chickens in Hong Kong in 1997 were highly pathogenic for chickens, and

although they replicated to low titer in experimentally infected ducks, they did not cause disease signs in these birds (11). The viruses isolated from ducks in the market were lethal for experimentally inoculated chickens (11). Alternatively, a previously avirulent influenza virus can acquire specific sequence changes, such as losing potential glycosylation sites or gaining multiple basic amino acid sequences in the connecting peptide of the HA, that confer virulence (12).

Avian influenza A viruses have been isolated from seals (13), whales (14), horses (15), and pigs (16). Sialic acid is the receptor for influenza viruses; the viral HA binds to the receptor. Avian and mammalian influenza viruses preferentially bind sialic acid molecules with specific oligosaccharide side chains with  $\alpha$ 2,3 and  $\alpha$ 2,6 linkages, respectively. Receptor specificity is thought to be an important determinant of host range. Reports of natural human infections with avian influenza viruses have been rare (with the notable exception of the 1997 Hong Kong H5N1 outbreak), and experimental infections have been difficult to achieve (17), leading to the view that avian influenza viruses are limited in their ability to replicate in human hosts. It was believed that avian influenza A viruses would have to acquire one or more genes from a human influenza A virus in order to cross the species barrier. The tracheal epithelium of pigs bears sialic acid molecules with both  $\alpha$ 2,3 and  $\alpha$ 2,6 linkages to galactose that can be infected with avian as well as mammalian influenza A viruses (18). Pigs that were simultaneously infected with avian and mammalian influenza A viruses were therefore proposed to be the intermediate hosts in which genetic reassortment would take place, giving rise to novel influenza A viruses with pandemic potential (19, 20).

Humans can be infected with swine influenza A viruses. Such infections are usually sporadic and tend to occur in individuals who are exposed to infected pigs (21). The infections can be severe, particularly in pregnant women (22) and immunocompromised hosts (23). Swine influenza infections rarely spread from person to person. A historic exception occurred on a military base in New Jersey in 1976, when a limited influenza outbreak was caused by a swine influenza A virus that was transmitted from person to person. One person died during this outbreak and several hundred infections were suspected, based on serosurveys of recruits. However, the outbreak did not spread (24).

## MORTALITY ASSOCIATED WITH INFLUENZA

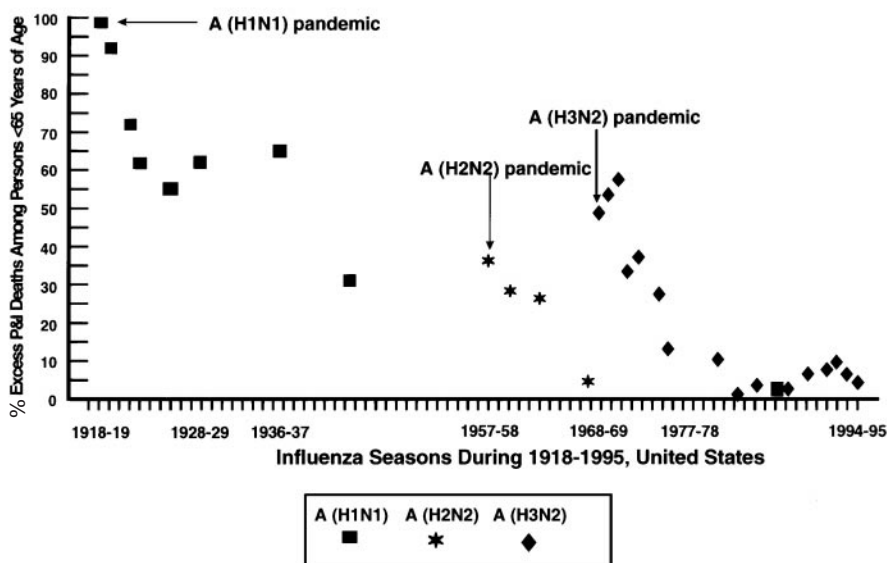
Increased mortality during influenza epidemics results not only from pneumonia and influenza but also from cardiopulmonary and other chronic diseases that can be exacerbated by influenza (25, 26). Quantification of deaths caused by influenza is complicated by the fact that death certificates may fail to list influenza as a primary, underlying, or contributory cause of death because a laboratory diagnosis was not made. Therefore, calculations of influenza-associated excess mortality (number of deaths above a statistical baseline of expected deaths) have been based both on excess deaths from pneumonia and influenza and on excess deaths from

all causes. Although excess mortality occurs primarily in the elderly, it can occur in all age groups, particularly among individuals who are at increased risk for complications of influenza.

Although the absolute number of deaths does not always distinguish a pandemic from severe nonpandemic seasons, the age distribution of influenza-related deaths has dramatically distinguished pandemics from the interpandemic seasons immediately preceding them. Persons under 65 years of age accounted for half of the influenza-related deaths in the United States during the 1968–1969 influenza pandemic, but far smaller proportions during the decades following the pandemic. A similar pattern was seen in the United States for all three pandemics of this century (Figure 1) (27). Thus, younger persons were at a 20-fold elevated risk for influenza-related mortality during a pandemic, whereas the elderly faced approximately the same risk during a pandemic as during later severe interpandemic seasons dominated by the same virus subtype.

## GLOBAL EPIDEMIOLOGY OF INTERPANDEMIC INFLUENZA

Global influenza surveillance indicates that influenza viruses are isolated every month from humans somewhere in the world. In temperate regions, influenza activity peaks during the winter months. In the Northern Hemisphere, influenza



**Figure 1** The age distribution of deaths in the United States associated with the three influenza pandemics of the twentieth century and the interpandemic seasons that followed each pandemic. (Reproduced with permission from Reference 27.)

outbreaks and epidemics typically occur between November and March, whereas in the Southern Hemisphere, influenza activity occurs between April and September. In tropical regions, influenza can occur throughout the year.

Although the epidemiology of influenza has been studied for many years, certain features—such as its seasonality, the precise mechanism for the emergence of new variants, and the factors that influence the spread of the disease—are not well understood. It is, however, generally accepted that influenza viruses are spread primarily by small-particle aerosols of virus-laden respiratory secretions that are expelled into the air by infected persons during coughing, sneezing, or talking. It is also generally accepted that direct person-to-person spread is the mechanism for maintenance of influenza viruses in the human population. There is no conclusive evidence for reintroduction of influenza viruses from latently or persistently infected individuals.

Global surveillance of influenza viruses has shown that antigenic variation and the consequent epidemiologic behavior of influenza A viruses follow a relatively uniform pattern. Each successive antigenic variant replaces its predecessor such that the co-circulation of distinct antigenic variants of a given subtype occurs for relatively short periods. During the past decade, new epidemic variants of influenza often are first detected in China before they spread to other locations (28, 29) (Figure 2).

An epidemic of influenza is an outbreak of disease in a circumscribed location, which may be a community, a city, or an entire country. Localized epidemics within a community often have a characteristic pattern in which the epidemic begins abruptly, peaks within 2 to 3 weeks, and has a total duration of 5 to 10 weeks (30). The spread of influenza through a community typically causes large increases in medical visits for febrile respiratory disease (31). During average epidemics, overall attack rates are estimated to be 10–20%, but in certain susceptible populations such as schoolchildren or nursing home residents, attack rates of 40–50% may occur.

Studies conducted during both pandemic years and interpandemic periods demonstrate that age-specific attack rates are often highest among schoolchildren (32). Family studies conducted in Houston (30, 33) and Seattle (34) documented age-specific attack rates during various epidemics during the 1970s and 1980s. Both studies demonstrated high rates of infection in school-age children and the importance of schoolchildren as vehicles of infection within families; however, the overall attack rates (24/100 people in Seattle and 33/100 people in Houston) and the age-specific rates in these two family studies differed somewhat. In the Houston study, the incidence of influenza among individuals in families with schoolchildren (38.5%) was more than double that in families without children attending school or day care. Furthermore, the Houston study demonstrated that the age distribution of culture-positive patients changes during the course of the epidemic. Initially, schoolchildren were culture positive, followed by a shift to preschool children and adults during the latter part of the epidemic (31). As a consequence, school absenteeism was often followed by employee absenteeism

during the influenza epidemics studied. Hospitalizations and influenza- and pneumonia-related deaths among the elderly often occurred during the latter part of the epidemic.

Epidemics that occur during interpandemic intervals are variable in size but are almost always smaller than those that follow introduction of a new virus subtype. The size of epidemics and their impact reflect the interplay between the extent of antigenic variation of the virus, the extent of immunity in the population, and the population groups that are most affected in a given year.

## HISTORY OF INFLUENZA PANDEMICS OF THE TWENTIETH CENTURY

Descriptions of epidemics and pandemics of respiratory disease with characteristics suggestive of influenza have been recorded for over four centuries. The rapid, global spread of pandemic influenza may be a relatively modern development related to increases in population and the growth of transportation systems necessary for the global transmission of the novel virus. Animals may have played a crucial role in past influenza epidemics as well as in modern pandemics. Outbreaks of respiratory disease among horses were recorded concurrently with outbreaks in humans during the eighteenth and nineteenth centuries, and in recent years it has been suggested that swine and birds are prominently involved in the generation of influenza pandemics.

### 1918–1919 Spanish Influenza A H1N1

The geographic origin of the virus that caused the pandemic of 1918–1919 is controversial. Some historians suggest that the virus originated in China; others suggest that it began circulating in March 1918 in midwestern US military camps. Subsequent outbreaks and epidemics of influenza with unprecedented virulence occurred almost simultaneously in North America, Europe, and Africa in August 1918 (35). This “second wave” of epidemic activity peaked by the end of October but was followed by yet another wave of disease in midwinter. Illness rates of nearly 40% were reported among schoolchildren during the autumn wave in the United States (36). For reasons that are not understood, the 1918 influenza A H1N1 pandemic was particularly severe. It caused many more deaths, particularly among young adults, than did the two subsequent pandemics of this century, even though the overall attack rate and the age distribution of cases in the 1918–1919 pandemic were not dramatically different from those observed during other pandemics (reviewed in 32).

Pathologic findings in fatal cases of “Spanish” influenza were variously described as acute inflammatory pulmonary edema, hemorrhagic pneumonitis, or pneumonia with acute hemorrhagic edema. Cyanosis of the skin was noted, particularly around the face, neck, and fingers, and the mouth and nares frequently

contained a brownish or reddish fluid. Thoracic cavities of victims contained varying amounts of light brown or yellow to dark red fluid. Lungs at postmortem were often large and distended, with the lower lobes most often affected. Dark, bloody, frothy fluid often poured out when lungs were sectioned (37). Many other patients succumbed to secondary bacterial infections and died with typical bacterial pneumonia (35).

### 1957–1958 Asian Influenza A H2N2

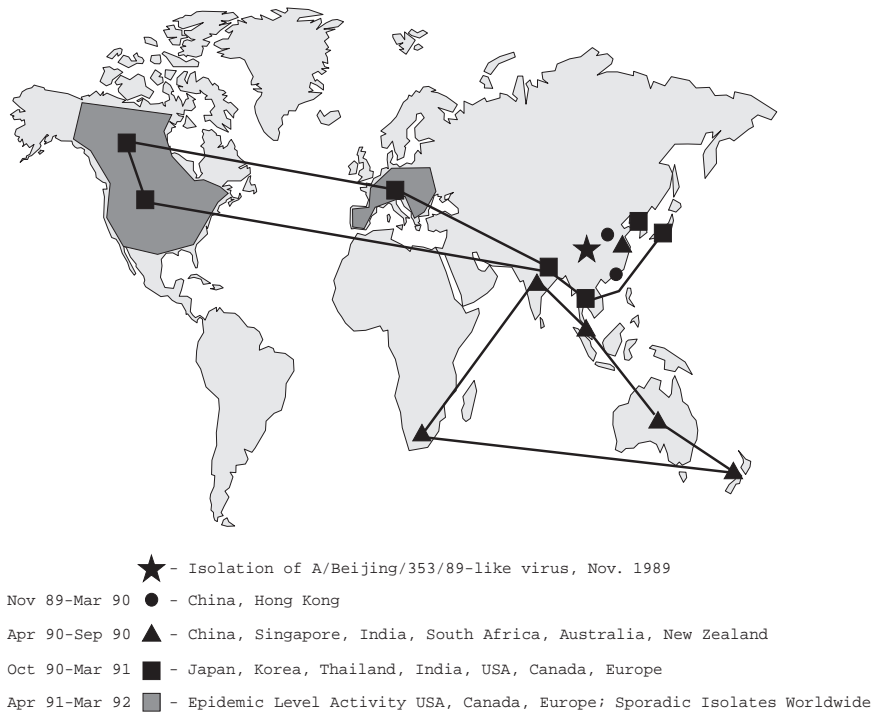
The Asian influenza pandemic of 1957 began in February in the southern Chinese province of Guizhou (formerly Kweichow). It spread in March to Hunan Province (formerly Yunan Province) and in April to Singapore and Hong Kong (38). The causative agent, an influenza A H2N2 virus, was first isolated in Japan in May 1957. This pandemic virus possessed completely different HA and NA antigens from the formerly circulating H1N1 viruses and rapidly spread worldwide by November 1957.

Although H2N2 viruses were first isolated in the United Kingdom and the United States in June or July of 1957, peak incidence of influenza caused by the new pandemic strain did not occur until October. This first wave of disease in both countries was followed by a second wave in January 1958; both waves were accompanied by excess mortality. The highest attack rates during this pandemic, >50%, occurred in children aged 5–19 (32). Total influenza-associated excess mortality during this pandemic was estimated at 69,800 (39).

### 1968 Hong Kong Influenza A H3N2

Viruses causing the influenza A H3N2 pandemic were first isolated in Hong Kong in July 1968. These viruses had a different HA but shared the N2 NA with previously circulating H2N2 viruses. Widespread disease with increased excess mortality was observed in the United States during the winter of 1968–1969, but in some other countries, including the United Kingdom, an epidemic did not occur until the winter of 1969–1970. Attack rates were highest (40%) among 10- to 14-year-old children. Total influenza-associated excess mortality for this pandemic was estimated at 33,800 in the United States (39). Many experts believe that the severity of the Hong Kong pandemic was reduced because much of the population had antibody to the N2 surface protein, which may have moderated the severity of infections.

Though not considered a true pandemic, the reemergence of influenza A H1N1 viruses in 1977 has had a significant influence on the epidemiology of influenza in recent years. The first outbreaks of disease were recorded in Tianjin (formerly Tientsin), China in May 1977 (reviewed in 38). These H1N1 viruses were nearly identical, both antigenically and genetically, to influenza H1N1 viruses that had circulated widely during the early 1950s. They spread to other parts of Asia and reached Russia by November 1977, then spread to Europe, North America, and the Southern Hemisphere. Attack rates of over 50% were observed among



**Figure 2** The emergence and spread of A/Beijing/353/89-like (H3N2) viruses, 1989–1991. Source: Centers for Disease Control and Prevention, Atlanta, GA.

schoolchildren, but illness occurred almost exclusively among persons younger than 20 years of age because older individuals had antibodies from their previous exposure to nearly identical viruses.

## ORIGIN OF THE PANDEMIC STRAINS OF THE TWENTIETH CENTURY

The objectives of molecular analysis of the strains of influenza that initiate pandemics are to determine where the virus came from and what made it so lethal. Phylogenetic analysis has identified evolutionarily related genes as a clue to the source of the virus. The initial focus is usually on genes that are thought to play a role in host range and pathogenesis.

The influenza pandemic of 1918–1919 is a matter of great interest to scientists and physicians because it was associated with several unique clinical features and took a devastating toll on human life worldwide. Serologic studies of individuals who had survived the pandemic and those born after it provided evidence that



the virus that caused the pandemic was an H1N1 virus (40). However, the origin of the virus was a mystery until recently because the pandemic predated the first successful isolation of influenza viruses.

Reid et al (41) have recovered viral RNA from formalin-fixed, paraffin-embedded tissues of two soldiers who died in 1918 and from a body exhumed from a mass grave in the permafrost of Alaska in 1918 (41). The first "case" was a 21-year-old male from South Carolina who was admitted to a hospital on September 20, 1918, with a diagnosis of influenza and pneumonia. He had a progressive clinical course with cyanosis and died six days later. Autopsy revealed lobar bacterial pneumonia of the left lung and focal acute bronchiolitis and alveolitis in the right lung, consistent with primary influenza pneumonia. The second "case" was a 30-year-old male from New York, who was admitted with a diagnosis of influenza on September 23, 1918, had a very rapid clinical course and died of acute respiratory failure three days later. Autopsy revealed massive bilateral pulmonary edema and focal acute bronchopneumonia. Fragments (120–200 nucleotides long) of influenza genes were recovered by reverse transcription and polymerase chain reaction (RT-PCR) using RNA extracted from the formalin-fixed, paraffin-embedded lung tissues of these two cases. The third "case" was that of an Inuit female of unknown age whose body was buried in the permafrost. Although there are no case records available regarding her illness and death, historical records indicate that influenza struck her village in November 1918, killing 72 people (85% of the adult population) in five days. Histologic examination of *in situ* biopsies of frozen lung tissues revealed acute massive pulmonary hemorrhage and edema; fragments of influenza genes were recovered from RNA extracted from the biopsy material.

Analyses of the nucleotide sequences of the fragments amplified from the first case indicate that each of the four genes examined was more closely related to the corresponding genes of mammalian influenza viruses than to those of avian influenza viruses (42). HA gene sequences from each of the three cases have been generated using up to 22 overlapping fragments and have been designated A/South Carolina/1/18, A/New York/1/18, and A/Brevig Mission/1/18, respectively (41). Further sequence analysis of the other genes is in progress (41).

Phylogenetic analysis of available H1 HA genes demonstrates three distinct clades (human, avian, and swine), which correspond to the sources of the viruses. The 1918 HA sequences are related to mammalian viruses and are placed at or near the root of the human and swine clades. The 1918 HA sequences are phylogenetically distinct from those of available avian viruses, although they resemble the avian consensus sequences in functionally important parts of the HA gene, such as antibody binding sites, glycosylation sites, and the receptor binding site. Plotting the total number of nucleotide changes against the year of isolation, Reid et al (41) suggest that an ancestor of the 1918 H1N1 virus entered the human population around 1915; a similar analysis using amino acid changes identifies this date as 1900. However, limitations of the available data set could have affected the outcome of the phylogenetic analysis. No human H1 HA sequences

are available for viruses circulating between 1918 and 1933, and there are only a limited number of these sequences from viruses isolated from 1933 to 1957. In addition, no pre-1975 avian H1 HA sequences are available.

Genetic studies have established that the influenza A H2N2 virus that caused the “Asian” influenza pandemic of 1957 derived its HA, NA, and a polymerase (PB1) gene from an avian influenza A virus (43). This pandemic strain is therefore thought to have arisen as a result of genetic reassortment between an avian influenza A virus and the circulating human influenza A (H1N1) virus.

Similarly, the H3N2 virus that caused the “Hong Kong” pandemic of 1968 was a reassortant virus that derived its HA and PB1 genes from an avian influenza virus and remaining gene segments from the circulating H2N2 virus (43).

## HUMAN H5N1 INFECTIONS

In May 1997, the Government Virus Unit in Hong Kong isolated an influenza A virus from the tracheal aspirate of a three-year-old child who was admitted with fever and respiratory symptoms and died of acute respiratory distress syndrome and Reye syndrome. The virus could not be subtyped using the World Health Organization (WHO) reagents prepared against circulating strains of influenza A H1N1 and H3N2 viruses and was subsequently identified as an H5N1 virus by the National Influenza Center in Rotterdam, The Netherlands (44). This identification was confirmed by WHO Collaborating Centers for Reference and Research on Influenza at the Centers for Disease Control and Prevention in Atlanta, Georgia (United States) and at the National Institute for Medical Research in London (United Kingdom) (45, 46). The initial investigation of this case focused on the following issues: the nature of the virus (avian, human, or a reassortant virus), the source of the virus, identification of additional infections, and molecular clues to explain the ability of the virus to jump the host species barrier.

Molecular characterization of the virus influenza A/Hong Kong/156/97 revealed that all eight gene segments were related to genes of avian influenza A viruses (45). Genetically similar influenza A H5N1 viruses had been isolated from sick chickens on farms in the New Territories of Hong Kong in March and April 1997 (46, 47), but there was no clear evidence linking the child with these farms. The kindergarten that the child attended had a nature court in which chicks and ducklings were kept; some of the chicks had become ill and died in the week preceding the child's illness. However, because the chicks and ducklings had died four months prior to the investigation, it was impossible to obtain samples that might have determined whether the birds were infected with influenza H5N1 viruses.

The HA gene is one of the genes that can determine host specificity and virulence. The connecting peptide of the HA gene contained an insertion of nucleotides coding for several basic amino acid residues (RERRRKKR). The presence

of multiple basic amino acids in the connecting peptide increases the range of tissues in an avian host that can be infected by avian influenza A viruses by making the HA cleavable by proteases other than the trypsin-like proteases. The role of the multi-basic cleavage site of the H5 HA in the pathogenesis of this human infection was unclear (45).

Six months later, 17 additional human H5N1 infections were identified in hospitalized patients in Hong Kong over a seven-week period (48). The patients ranged in age from 1 to 60 years, and 7 were male. Six of the 18 patients died; with the exception of the first case, the illnesses in children were milder than in adults. The clinical features of 12 of the cases were reported (49). Influenza A was isolated from 16 of the 18 cases; two were diagnosed serologically. Molecular analysis established that all gene segments of the viruses were avian in origin and that reassortment with human influenza A viruses had not occurred (45).

There was a concurrent outbreak of influenza in chickens in the Hong Kong markets (11). Similar viruses were also recovered from asymptomatic ducks and geese from the same markets (11). The viruses isolated from the live-bird markets were genetically identical to the viruses isolated from the human cases (50). The receptor specificity of the human and avian isolates was similar (51), indicating that this property alone would not limit the host range of avian influenza A viruses.

Molecular and epidemiologic results obtained during this investigation suggest that the human H5N1 infections resulted from poultry-to-human spread and that person-to-person spread was rare and inefficient (48). Thus, although the avian influenza A H5N1 viruses were able to cross the host species barrier and infect humans, they were not efficiently transmitted. It is possible that the virus would have become more efficiently transmissible if it acquired mutations in specific gene segments to adapt to the human host, or if the virus acquired one or more gene segments of human influenza A virus by reassortment. However, the closure and depopulation of the live-bird markets of Hong Kong in December 1997 was followed by intensive surveillance of H5N1 infection in live birds imported into Hong Kong, and no further cases of human H5N1 infection have occurred since then.

This incident established for the first time that avian influenza A viruses could cause an outbreak of disease in humans without passing through an intermediate host. By inference, it follows that reassortment with human influenza A viruses could occur in a human host co-infected with avian and human influenza A viruses, without the postulated intermediate host.

## HUMAN H9N2 INFECTIONS

In March 1999, the Government Virus Unit in Hong Kong isolated influenza A viruses that could not be subtyped as H1 or H3 from two children with self-limiting febrile upper respiratory infections (52, 52a). These viruses were iden-

tified as influenza A H9N2 viruses at the WHO Collaborating Center at Mill Hill, United Kingdom; the findings were confirmed by the WHO Collaborating Center at the Centers for Disease Control and Prevention, Atlanta, Georgia. Ongoing influenza surveillance in the live-bird markets of Hong Kong, which began during the H5N1 outbreak in 1997, had identified a high prevalence of H9N2 infections in chickens, often in association with H5N1 infections (53). Molecular analyses indicate that the HA and NA genes of the human H9N2 isolates are avian in origin (52). An epidemiologic investigation of the two cases is in progress to establish the source of the infection and to identify additional infections.

## CONCLUSIONS

During the past two decades, several widely held concepts concerning the epidemiology of influenza were demonstrated to be false. It was previously believed that influenza pandemics occurred at 10- to 14-year intervals, but it has been over 30 years since H3N2 viruses appeared. Furthermore, reclassification of influenza A viruses indicates that H1N1 viruses circulated from at least 1918 until 1957. Thus, it is now clear that influenza pandemics occur at unpredictable intervals. It was also believed that concurrent circulation of two different influenza A subtypes did not occur. However, H1N1 and H3N2 viruses have been circulating together since 1977. Finally, receptor specificity was believed to provide a barrier against human infection by avian influenza viruses that differ in this property from their human counterparts. This belief has been modified by the recently documented human infections by avian H5N1 and H9N2 viruses in Hong Kong.

Although a great deal has been learned about influenza viruses and the disease they cause, many important, unanswered questions remain. For example, it is not known precisely how new pandemic strains of influenza arise or how pandemics begin. In addition, many questions remain unanswered about interpandemic influenza. We do not yet understand the exact nature of the changes that must occur during antigenic drift in order to generate a new epidemic strain. It is also not known whether a particular antigenic variant can arise simultaneously in two or more locations as a result of antibody pressure in the population. Furthermore, it is not known whether influenza viruses migrate between the Northern and Southern Hemispheres to become epidemic in the respective temperate zones during the cold-weather season, or whether influenza viruses are perpetuated and seeded in the population during the summer months. Future studies are necessary to answer these questions about influenza, an important cause of medically attended acute respiratory illness.

**Visit the Annual Reviews home page at [www.AnualReviews.org](http://www.AnualReviews.org).**

## LITERATURE CITED

1. Smith W, Andrewes CH, Laidlaw PP. 1933. A virus obtained from influenza patients. *Lancet* ii:66–88
2. Francis TJ. 1940. New type of virus from epidemic influenza. *Science* 91:405–8
3. Ina Y, Gojabori T. 1994. Statistical analysis of nucleotide sequences of the hemagglutinin gene of human influenza A viruses. *Proc. Natl. Acad. Sci. USA* 91:8388–92
4. Fitch WM, Bush RM, Bender CA, et al. 1997. Long term trends in the evolution of H(3) HA1 human influenza type A. *Proc. Natl. Acad. Sci. USA* 94:7712–18
5. Webster RG, Yakhno M, Hinshaw VS, et al. 1978. Intestinal influenza: replication and characterization of influenza viruses in ducks. *Virology* 84:268–78
6. Bean WJ, Schell M, Katz J, et al. 1992. Evolution of the H3 influenza virus hemagglutinin from human and nonhuman hosts. *J. Virol.* 66:1129–38
7. Webster RG, Bean WJ Jr. 1998. Evolution and ecology of influenza viruses: interspecies transmission. In *Textbook of Influenza*, ed. KG Nicholson, RG Webster, AJ Hay, pp. 109–19. Oxford, UK: Blackwell
8. Webster RG, Bean WJ, Gorman OT, et al. 1992. Evolution and ecology of influenza A viruses. *Microbiol. Rev.* 56:152–79
9. Halvorson D, Karunakaran D, Senne D, et al. 1983. Epizootiology of avian influenza—simultaneous monitoring of sentinel ducks and turkeys in Minnesota. *Avian Dis.* 27:77–85
10. Ito T, Kawaoka Y. 1998. Avian influenza. In *Textbook of Influenza*, ed. KG Nicholson, RG Webster, AJ Hay, pp. 126–36. Oxford, UK: Blackwell
11. Shortridge KF, Zhou NN, Guan Y, et al. 1998. Characterization of avian H5N1 influenza viruses from poultry in Hong Kong. *Virology* 252:331–42
12. Horimoto T, Rivera E, Pearson J, et al. 1995. Origin and molecular changes associated with emergence of a highly pathogenic H5N2 influenza virus in Mexico. *Virology* 213:223–30
13. Geraci JR, St. Aubin DJ, Barker IK, et al. 1982. Mass mortality of harbor seals: pneumonia associated with influenza A virus. *Science* 215:1129–31
14. Hinshaw VS, Bean WJ, Geraci J, et al. 1986. Characterization of two influenza A viruses from a pilot whale. *J. Virol.* 58: 655–56
15. Guo Y, Wang M, Kawaoka Y, et al. 1992. Characterization of a new avian-like influenza A virus from horses in China. *Virology* 188:245–55
16. Guan Y, Shortridge KF, Krauss S, et al. 1996. Emergence of avian H1N1 influenza viruses in pigs in China. *J. Virol.* 70:8041–46
17. Beare AS, Webster RG. 1991. Replication of avian influenza viruses in humans. *Arch. Virol.* 119:37–42
18. Cox NJ, Kawaoka Y. 1998. Orthomyxoviruses: influenza. In *Topley and Wilson's Microbiology and Microbial Infections*, ed. BWJ Mahy, L Collier, 1:385–433. London: Arnold
19. Scholtissek C, Burger H, Kistner O, et al. 1985. The nucleoprotein as a possible major factor in determining host specificity of influenza H3N2 viruses. *Virology* 147:287–94
20. Ito T, Couceiro JN, Kelm S, et al. 1998. Molecular basis for the generation in pigs of influenza A viruses with pandemic potential. *J. Virol.* 72:7367–73
21. Wentworth DE, Thompson BL, Xu X, et al. 1994. An influenza A (H1N1) virus, closely related to swine influenza virus, responsible for a fatal case of human influenza. *J. Virol.* 68:2051–58
22. McKinney WP, Volkert P, Kaufman J. 1990. Fatal swine influenza pneumonia

- during late pregnancy. *Arch. Intern. Med.* 150:213–15
23. Patriarca PA, Kendal AP, Zakowski PC, et al. 1984. Lack of significant person-to-person spread of swine influenza-like virus following fatal infection in an immunocompromised child. *Am. J. Epidemiol.* 119:152–58
  24. Dowdle WR, Millar JD. 1978. Swine influenza: lessons learned. *Med. Clin. N. Am.* 62:1047–57
  25. Collins SD. 1932. Excess mortality from causes other than influenza and pneumonia during influenza epidemics. *Public Health Rep.* 47:2159
  26. Eickhoff TC, Sherman IL, Serfling RE. 1961. Observations on excess mortality associated with epidemic influenza. *JAMA* 176:776–82
  27. Simonsen L, Clarke MJ, Schonberger LB, et al. 1998. Pandemic versus epidemic influenza mortality: a pattern of changing age distribution. *J. Infect. Dis.* 178:53–60
  28. Cox NJ, Brammer TL, Regnery HL. 1994. Influenza: global surveillance for epidemic and pandemic variants. *Eur. J. Epidemiol.* 10:467–70
  29. Cox NJ, Regnery HL. 1996. Global influenza surveillance: tracking a moving target in a rapidly changing world. In *Options for the Control of Influenza III, Cairns, Australia*, ed. LE Brown, AW Hampson, RG Webster, pp. 591–98. Amsterdam: Elsevier
  30. Glezen WP, Couch RB. 1978. Interpandemic influenza in the Houston area, 1974–76. *N. Engl. J. Med.* 298:587–92
  31. Glezen WP. 1982. Serious morbidity and mortality associated with influenza epidemics. *Epidemiol. Rev.* 4:25–44
  32. Glezen WP. 1996. Emerging infections: pandemic influenza. *Epidemiol. Rev.* 18:64–76
  33. Taber LH, Paredes A, Glezen WP, et al. 1981. Infection with influenza A/Victoria virus in Houston families, 1976. *J. Hyg.* 86:303–13
  34. Fox JP, Hall CE, Cooney MK, et al. 1982. Influenza virus infections in Seattle families, 1975–1979. I. Study design, methods and the occurrence of infections by time and age. *Am. J. Epidemiol.* 116:212–27
  35. Crosby AW. 1989. *America's Forgotten Pandemic*. Cambridge, UK: Cambridge Univ. Press
  36. Frost WH. 1919. The epidemiology of influenza. *JAMA* 73:313–18
  37. Walker OJ. 1919. Pathology of influenza pneumonia. *J. Lab. Clin. Med.* 5:154–75
  38. Stuart-Harris CH, Schild GC, Oxford JS. 1985. *Influenza. The Viruses and the Disease*, pp. 118–38. Victoria, Can.: Edward Arnold. 2nd ed.
  39. Noble GR. 1982. Epidemiological and clinical aspects of influenza. In *Basic and Applied Influenza Research*, ed. AS Beare, pp. 11–50. Boca Raton, FL: CRC
  40. Shope RE. 1936. The incidence of neutralizing antibodies for swine influenza virus in the sera of human beings of different ages. *J. Exp. Med.* 63:669–84
  41. Reid AH, Fanning TG, Hultin JV, et al. 1999. Origin and evolution of the 1918 “Spanish” influenza virus hemagglutinin gene. *Proc. Natl. Acad. Sci. USA* 96:1651–56
  42. Taubenberger JK, Reid AH, Krafft AE, et al. 1997. Initial genetic characterization of the 1918 “Spanish” influenza virus. *Science* 275:1793–96
  43. Kawaoka Y, Krauss S, Webster RG. 1989. Avian-to-human transmission of the PB1 gene of influenza A viruses in the 1957 and 1968 pandemics. *J. Virol.* 63:4603–8
  44. de Jong JC, Claas EC, Osterhaus AD, et al. 1997. A pandemic warning? [letter]. *Nature* 389:554
  45. Subbarao K, Klimov A, Katz J, et al. 1998. Characterization of an avian influenza A (H5N1) virus isolated from a child with a fatal respiratory illness. *Science* 279:393–96
  46. Claas EC, Osterhaus AD, van Beek R, et

- al. 1998. Human influenza A H5N1 virus related to a highly pathogenic avian influenza virus. *Lancet* 351:472–77. Erratum, 351:(9111):1292
47. Suarez DL, Garcia M, Latimer J, et al. 1999. Phylogenetic analysis of H7 avian influenza viruses isolated from the live bird markets of the Northeast United States. *J. Virol.* 73:3567–73
48. Mounts AW, Kwong H, Izurieta HS, et al. 1999. Case-control study of risk factors for avian influenza A (H5N1) disease, Hong Kong, 1997. *J. Infect. Dis.* 180:505–8
49. Yuen KY, Chan PK, Peiris M, et al. 1998. Clinical features and rapid viral diagnosis of human disease associated with avian influenza A H5N1 virus. *Lancet* 351:467–71
50. Zhou NN, Shortridge KF, Claas ECJ, et al. 1999. Rapid evolution of H5N1 influenza viruses in chickens in Hong Kong. *J. Virol.* 73:3366–74
51. Matrosovich M, Zhou N, Kawaoka Y, et al. 1999. The surface glycoproteins of H5 influenza viruses isolated from humans, chickens, and wild aquatic birds have distinguishable properties. *J. Virol.* 73:1146–55
52. Anonymous. 1999. Influenza. *Wkly. Epidemiol. Rec.* 74:111
- 52a. Periris M, Yuen KY, Leung CW, et al. 1999. Human infection with influenza H9N2. *Lancet* 354:916–17
53. Guan Y, Shortridge KF, Krauss S, Webster RG. 1999. Molecular characterization of H9N2 influenza viruses: Were they the donors of the “internal” genes of H5N1 viruses in Hong Kong? *Proc. Natl. Acad. Sci.* 96:9363–67







## CONTENTS

Inferior Vena Cava Interruption: How and When?, <i>Philippe Girard, Bernard Tardy, Hervé Decousus</i>	1
Ductal Carcinoma In Situ of the Breast, <i>Melvin J. Silverstein</i>	17
Gene Therapy for Adenosine Deaminase Deficiency, <i>Robertson Parkman, Kenneth Weinberg, Gay Crooks, Jan Nolta, Neena Kapoor, Donald Kohn</i>	33
Acupuncture: An Evidence-Based Review of the Clinical Literature, <i>David J. Mayer</i>	49
Role of Telomerase in Cell Senescence and Oncogenesis, <i>Virginia Urquidi, David Tarin, Steve Goodison</i>	65
Coronary Artery Disease in the Transplanted Heart, <i>M. Weis, W. von Scheidt</i>	81
Measures of Success and Health-Related Quality of Life in Lower-Extremity Vascular Surgery, <i>Joe Feinglass, Mark Morasch, Walter J. McCarthy</i>	101
New Horizons in the Treatment of Autoimmune Diseases: Immunoablation and Stem Cell Transplantation, <i>Alberto M. Marmont</i>	115
The Surgical Treatment of Parkinson's Disease, <i>Kenneth A. Follett</i>	135
Atherogenic Lipids and Endothelial Dysfunction: Mechanisms in the Genesis of Ischemic Syndromes, <i>Mark R. Adams, Scott Kinlay, Gavin J. Blake, James L. Orford, Peter Ganz, Andrew P. Selwyn</i>	149
Management of Patients with Hereditary Hypercoagulable Disorders, <i>C. Kearon, M. Crowther, J. Hirsh</i>	169
Neurocysticercosis: Updates on Epidemiology, Pathogenesis, Diagnosis, and Management, <i>A. Clinton White Jr.</i>	187
Anti-Cytokine Therapy for Rheumatoid Arthritis, <i>R. N. Maini, P. C. Taylor</i>	207
Artificial Skin, <i>J. T. Schulz III, R. G. Tompkins, J. F. Burke</i>	231
Age-Associated Increased Interleukin-6 Gene Expression, Late-Life Diseases, and Frailty, <i>William B. Ershler, Evan T. Keller</i>	245
Streptococcal Toxic Shock Syndrome Associated with Necrotizing Fasciitis, <i>Dennis L. Stevens</i>	271
Role of Cytokines in the Pathogenesis of Inflammatory Bowel Disease, <i>Konstantinos A. Papadakis, Stephan R. Targan</i>	289
Anorexia and Bulimia Nervosa, <i>W. H. Kaye, K. L. Klump, G. K. W. Frank, M. Strober</i>	299
The Role of Protein Traffic in the Progression of Renal Diseases, <i>Piero Ruggenenti, Giuseppe Remuzzi</i>	315
Carotid Artery Dissection, <i>C. Stapf, M. S. V. Elkind, J. P. Mohr</i>	329
Bacterial Vaginosis, <i>Jack D. Sobel</i>	349
Current Concepts in Cobalamin Deficiency, <i>Ralph Carmel</i>	357
Adjuvant Therapy for Breast Cancer, <i>G. Hortobagyi</i>	377
Kidney Transplantation from Living Unrelated Donors, <i>J. Michael Cecka</i>	393
Global Epidemiology of Influenza: Past and Present, <i>N. J. Cox, K. Subbarao</i>	407
The Spectrum of Human Herpesvirus 6 Infection: From Roseola Infantum to Adult Disease, <i>Mark Young Stoeckle</i>	423

Catheter Ablation for Atrial Fibrillation, <i>Pierre Jaïs, Dipen C. Shah, Michel Haïssaguerre, Meleze Hocini, Jing Tian Peng, Jacques Clémenty</i>	431
Genetic Disorders Affecting Proteins of Iron Metabolism: Clinical Implications, <i>Sujit Sheth, Gary M. Brittenham</i>	443
Genetics of Psychiatric Disease, <i>Wade H. Berrettini</i>	465
The Marfan Syndrome, <i>Reed E. Pyeritz</i>	481
Nonsteroidal Anti-Inflammatory Drugs and Cancer Prevention, <i>John A. Baron, Robert S. Sandler</i>	511
Lymphatic Mapping and Sentinel Lymph Node Biopsy in Patients with Breast Cancer, <i>Charles E. Cox, Siddharth S. Bass, Christa R. McCann, Ni Ni K. Ku, Claudia Berman, Kara Durand, Monica Bolano, Jessica Wang, Eric Peltz, Sarah Cox, Christopher Salud, Douglas S. Reintgen, Gary H. Lyman</i>	525
The Genetics of the Amyloidoses, <i>Joel N. Buxbaum, Clement E. Tagoe</i>	543