INFECTIOUS DISEASE EPIDEMIOLOGY: THEORY AND PRACTICE

Second Edition

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CHAPTER FIFTEEN

EPIDEMIOLOGY AND PREVENTION OF INFLUENZA

Mark C. Steinhoff

Introduction

Influenza virus has a unique epidemiology with two aspects: (1) annual seasonal epidemics of respiratory disease with attack rates of 10% to 30% in all regions of the world, and (2) the classical emerging infection, causing global pandemics when new antigenic variants emerge. Influenza viruses are epizootic in avian and animal species, and analyses of nucleic acid sequences suggest that human influenza A viruses derive from avian influenza viruses. The antigenic variation of this virus is the key to its ability to cause annual epidemics and periodic pandemics. The genetic and molecular aspects of antigenic variation will be described in relation to the unique epidemiology of this virus. Because antigenic change is random and not predictable, the influenza virus will continue to cause widespread epidemics, although many aspects of the epidemiology and variability of this virus are understood and effective antivirals and vaccines are available. Current control strategies require reevaluation to achieve a true reduction in the toll of influenza morbidity and mortality, and enhanced pandemic preparedness is essential.

Clinical Features of Influenza

The word *influenza* is from the Italian (derived from Latin *influentia*), referring to the influence of the stars, reflecting ancient concepts of the causation of influenza epidemics. The clinical disease influenza is familiar, because everyone has been infected. It is characterized by an abrupt onset of fever and respiratory symptoms, including rhinorrhea, cough, and sore throat. Myalgia and headache are more common with influenza than with other respiratory viral infections, and the malaise and prostration of this disease are well known. Gastrointestinal symptoms are not common in adults, but 50%

of infants and children may have vomiting, abdominal pain, and diarrhea with influenza. Influenza disease is usually self-limited, lasting for 3 to 5 days, but complications, which are more frequent in the elderly and persons with chronic illnesses, can prolong illness. Some patients may develop a primary influenza viral pneumonia, which can be fatal. More commonly, a secondary bacterial pneumonia may occur up to 2 weeks after the acute viral infection.[3a,3b] In infants and children, otitis media and croup are common complications. Other less frequent complications include myocarditis, myositis, and encephalitis. Reye's syndrome, a hepatic and CNS complication seen in children, is associated with the use of aspirin and other salicylates.

Transmission

Influenza virus spreads through respiratory secretions of infected persons, which may contain up to 10^5 virus particles/mL. An infected person generates infectious aerosols of secretions during coughing, sneezing, and talking. In addition, infectious secretions are spread by direct (by kissing) or indirect (by nose-finger-doorknob) contact with respiratory mucosa. The inhaled virus attaches to columnar epithelial cells of the upper respiratory tract and initiates a new infection in the host. The incubation period is from 1 to 4 days, and infected hosts are capable of transmitting the virus from shortly before the onset of clinical disease up to the fourth or fifth day of illness.

Diagnosis

Because of the clinical similarity of influenza virus infection to the manifestations of other respiratory viral infections, influenza virus infection cannot be reliably diagnosed from clinical signs and minor symptoms.[4] Although some clinicians and many laypersons use the term *flu* or *influenza* to describe respiratory illness, only viral culture or serology can prove the presence of influenza virus. Culture requires nasal or throat secretions obtained within 3 days of onset, which are then cultured in embryonated hens' eggs or tissue culture. Viral growth occurs in 2 to 3 days, after which the virus is identified using reagents for type and subtype. Influenza virus can also be identified rapidly within several hours in clinic settings using rapid antigen detection methods, such as immunofluorescence or enzyme-linked immunosorbent assay (ELISA) and other techniques. Infection is proven by serology to show a four-fold increase in antibodies to influenza virus and requires acute and convalescent blood specimens obtained approximately 3 weeks apart. Standard techniques for detection of influenza antibodies include hemagglutination inhibition (HI), complement fixation (CF), and ELISA techniques.

The Virus

Influenza virus was one of the first human viruses to be cultured and studied. In 1933, Wilson Smith, Andrews, and Laidlaw in the United Kingdom first isolated human influenza A virus from a ferret (infected by secretions from an ill Andrews).[1] Burnet developed the technique of culture in hens' eggs in 1936, which enabled study of the viruses and the development of vaccines. Influenza B virus was isolated in 1940, and type C virus in 1947.[2]

Influenza type A and B viruses contain eight segments of single-stranded RNA that code for 10 separate proteins. Influenza type C has seven RNA segments and a single surface glycoprotein. Table 15-1 summarizes the gene segments and their associated proteins. The hemagglutinin (HA) and neuraminidase (NA) are surface glycoproteins that are important in both pathogenesis and immune protection from infection. The HA functions as the attachment protein, mediating attachment to sialic acid-containing glycoproteins on columnar epithelial cells of the respiratory tract. HA has a binding site that is highly conserved and surrounded by five specific antigenic epitopes that manifest rapid changes. Specific antibody to these HA epitopes prevents attachment and entry of influenza viruses into host cells. HA specificity for receptor binding is a determinant of which species can be infected, or host range.[3] The HA is also a virulence determinant. The HA protein must be cleaved into H1 and H2 proteins by host proteases to create a hydrophobic tail necessary for fusion of viral and host cell membranes. The host proteases are found in human respiratory and avian enteric tissues. In avian viruses, the introduction of basic amino acids near the HA cleavage site permits cleavage by proteases of other tissues, which allows viral infection of vascular, central nervous system, and other tissues (pantropism) and a dramatic increase in virulence. The NA cleaves sialic acid residues to allow virus release from the host epithelial cell; specific anti-NA antibody presumably diminishes release of virons from host cells.

The subtypes of influenza A virus are determined by these two surface antigens. Among influenza A viruses that infect humans, three different HA subtypes have classically been described—H1, H2, and H3. H5, H7, and H9 have also recently been shown to infect humans.

TABLE 15-1 The Genes of Influenza A Virus and Their Protein Products

RNA Segment Number	Gene Product	Protein	Proposed Functions of Protein
1	PB1	Polymerase	RNA transcriptase
2	PB2	Polymerase	RNA transcriptase (host range determinant)
3	PA	Polymerase	RNA transcriptase
4	HA	Hemagglutinin	Viral attachment to cell membranes; major antigenic and virulence determinant
5	NA	Neuraminidase	Release from membranes; major antigenic determinant
6	NP	Nucleoprotein	Encapsidates RNA, type-specific antigen
7	M1	Matrix	Surrounds viral core; involved in assembly and budding
	M2	Ion channel	
8	NS1	Nonstructural	RNA binding, anti-interferon
	NS2	Nonstructural	Unknown

Nomenclature

The nomenclature of influenza viruses is necessarily somewhat complex because of the need to name all new strains. Virus strains are named with (1) the virus type, (2) the geographic site of first identification of the specific virus, (3) the strain number from the isolating laboratory, (4) the year of virus isolation, and (5) the virus subtype (for influenza A). For example, one of the viruses in the influenza vaccine that was recently recommended for 2004–2005 is A California/7/2004(H3N2). This refers to a type A virus first isolated in California in 2004, as laboratory strain number 7, which is subtype H3N2. The early isolate of influenza is A/WS(WilsonSmith)/33/H1N1.

Epidemiology

Epidemics and Pandemics

The influenza virus causes annual epidemics of disease, and it caused three global pandemics in the 20th century (*pandemic* from the Greek: *pan* = all, *demos* = people). Pandemics of febrile respiratory disease that resemble influenza have been described since the days of Hippocrates (Table 15-2). The characteristic pattern of an influenza pandemic is initiation from a single geographic focus (often in Asia) and rapid spread, often along routes of travel. High attack rates of all age groups are observed. Although case fatality rates are usually not increased substantially, because of the very large number of infections and cases, the number of hospitalizations and deaths are unusually high. In a pandemic, multiple waves of infections can sweep through a community, each wave infecting sectors of the population different from those affected in the initial pandemic episode.

TABLE 15-2 A Century of Antigenic Shifts of Influenza A Virus

Years	Virus Description	Antigenic Change (Source)	Pandemic
1889	H3N2*	Not known	Severe
1900	H3N8*	Not known	Moderate
1918→1956	H1N1 "Spanish"*	HA, NA (? avian)	Major; 50 million deaths in first year
1957→1968	H2N2 "Asian"	New HA, NA, PB1 (avian)	Severe
1968→	H3N2 "Hong Kong"	New HA,† PB1 (avian)	Moderate
1977→	H1N1 "Russian"	Apparently identical with 1956 H1N1‡	Relatively mild§

Notes: *Data derived from serology; pandemic virus not available for study because influenza virus was first cultured in 1933.
†New human H3HA varied by only six amino acids from parent avian H3HA, with all changes at sites important for receptor binding and antigenicity.
‡May have escaped from a laboratory.
§Those aged more than 22 years had antibody from 1918–1956 H1N1 strain.

The 1918 Spanish influenza pandemic had an attack rate of 20% to 30% in adults, and 30% to 45% in children. The case fatality rate in adults was as high as 15% to 50%, with an unusual occurrence of deaths in young adults (Figure 15-1). It is estimated that at least 20 to 50 million persons died in a single year in this global pandemic, many of them young adults (see text box, "1918 Pandemic Flu").

Annual local epidemics follow a fairly predictable pattern.[5] In North America, epidemics usually occur between November and March, manifested first by high rates of school and industrial absenteeism, followed by an increase in visits to health care facilities, an increase in pneumonia and influenza hospital admissions, and finally an increase in deaths from pneumonia or influenza.[5] In any single locality, epidemic influenza often begins abruptly, reaches a peak within 3 weeks, and usually ends by 8 weeks. A city or region can experience two sequential or overlapping epidemics with different strains of viruses in a single winter. Epidemics in the Southern Hemisphere usually occur in the May to September winter season; in some cases, they are caused by the new strain of epidemic virus that will cause epidemics in the Northern Hemisphere the following winter. In the tropics, disease seasonality can be associated with monsoons, or a year-round isolation of influenza virus may be observed.[6,6a,6b] Virus spread during the winter season is said to be favored by the fact that virus survives better in environments of lower temperature and humidity. In tropical areas, spread during the monsoon suggests that indoor crowding caused by weather may be a more important factor.

In general, rates of infection in infants and children are higher than those of adults, and the rates of hospitalization are highest in infants and lower in children and high in the elderly.[6c,6d] Families with school-aged children have

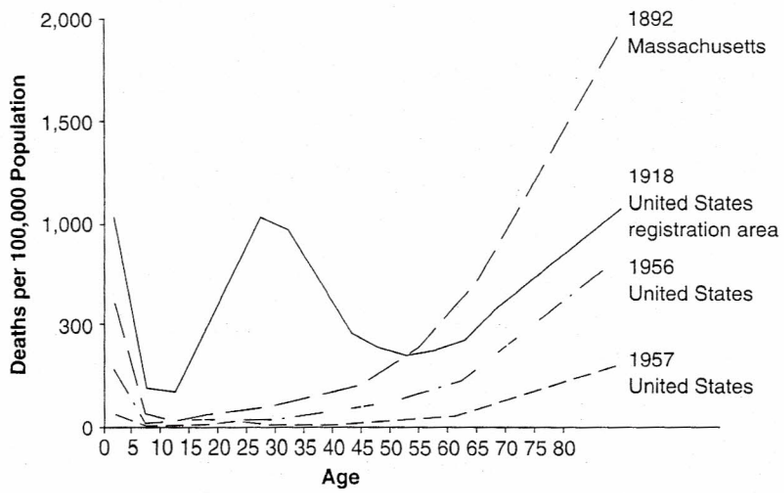


FIGURE 15-1 Age distribution of mortality of selected influenza epidemics in the United States. Note the difference between the 1918 pandemic with high young adult mortality rates and other epidemics with higher mortality at the extremes of the age spectrum.
Source: C.C. Dauer and R.E. Sterling, 1961, Mortality from Influenza, *American Review of Respiratory Diseases*, Vol. 82, Supplement, pp. 15–26. Official Journal of the American Thoracic Society, © American Lung Association.

the highest rates of infection.[6b] These observations suggest that relatively immunologically naive children are important in the spread of epidemic strains. Table 15-3 summarizes recent US data on rates for hospitalization for influenza.

Each epidemic and pandemic varies in size and impact, determined by the degree of the antigenic variation of the new virus, its virulence, and the level of existing protective immunity in the infected population. (See Table 15-2, noting the association between the degree of antigenic difference and the size of the pandemic.) During average epidemics in North America, attack rates are often 10% to 20% in large populations, although certain population groups (e.g., school children or nursing home residents) and local outbreaks can have attack rates of 40% to 50%. More than 20,000 influenza-associated excess deaths occurred in the United States during each of nine epidemics between 1972 and 1991, and more than 40,000 deaths occurred during three of them. Recent analyses suggest the annual winter increase in all mortality is substantially due to influenza.[7] Persons aged more than 65 years account for 90% of the excess deaths associated with annual epidemics. Although pandemics cause many deaths over one or two winters, mortality from an emergent influenza strain is by no means restricted to the first two years after a new strain emerges. The cumulative deaths during successive annual epidemics of an interpandemic period often exceed the death in the pandemic period. For example, it has been estimated that the H3N2 virus in its first pandemic in 1968–1969 caused 34,000 deaths in the United States, but it has caused more than 300,000 deaths in the annual epidemics in the subsequent 21 years during which it has circulated (from 1969 until the early 1990s). Not only does influenza have a large impact on mortality, morbidity from influenza is significant. Since the 1990s, annual influenza has been associated with an average of 226,000 hospitalizations per year in the United States.[7a]

Surveillance for influenza disease and for specific influenza viruses is necessary to track epidemic disease, to detect pandemics, and to determine virus serotypes for vaccine policy. In the United States, the Centers for Disease Control and Prevention (CDC) uses several surveillance systems.

TABLE 15-3 Influenza Disease by Age Group

	Rate of Hospitalization/100,000	
Age (years)	**Normal**	**High Risk**
0–11 mo	496–1038	1900
1–2	186	800
3–4	86	320
5–14	8–41	92
15–44	20–30	56–110
45–64	13–23	392–635
≥65	125–228	399–518

Source: MMWR, Vol. 52, RR06-, 2004; 1-40. Centers for Disease Control and Prevention.

1. A sentinel physician surveillance network, utilizing a simple clinical definition of influenza-like illness (ILI); a fever greater than 100°F, plus cough or sore throat. Approximately 1000 physicians each week from October through May record the total number of patient visits for the week, and the number of patients examined for influenza-like illness by age group.
2. The collaborating laboratory surveillance system of 75 World Health Organization (WHO) collaborating laboratories and 50 other laboratories in the United States from October through May report the total number of specimens received for respiratory virus testing and the number of positive isolates of influenza virus.
3. The 122-city mortality reporting system includes selected cities with a population of more than 100,000 that provide data on the percentage of deaths listed with pneumonia or influenza as the underlying cause or as being associated with influenza.
4. State and territorial epidemiologists report influenza activity levels. Each state epidemiologist reports the estimated level of influenza activity as no activity or sporadic (sporadically occurring cases of ILI or culture-confirmed influenza [CCI] without school or institutional outbreaks), regional (outbreaks of ILI or CCI in counties that total less than 50% of the state population), or widespread activity (outbreaks of ILI or CCI in counties that are larger than 50% of the total state population).
5. Influenza pediatric mortality and morbidity are reported; deaths in children younger than 18 years is a new reportable death category.
6. In 10 states admissions related to influenza in children are reported.
7. Reports of influenza child hospitalization in single counties in three states provide true incidence data.[17] These data are summarized in the *Morbidity and Mortality Weekly Report* (*MMWR*) from the CDC and are found on its Web site.

Mechanisms of Antigenic Variation

Because most epidemic and all 20th-century pandemic infections by influenza virus are type A, the following discussion will focus on type A influenza. Although indistinguishable from type A in an individual patient, type B influenza disease is usually less severe, and it does not appear to cause pandemics. Type C disease is generally mild and not associated with widespread epidemics or pandemics.

The mutability or antigenic variation of influenza virus has been described by the term *antigenic drift*, denoting minor antigen changes through mutations, and *antigenic shift* describes major genetic and antigenic changes through reassortment.

Antigenic drift describes the frequent minor antigenic changes in the HA and NA surface antigens that account for the annual epidemics. Antigenic drift is ascribed to the relatively high rate of spontaneous mutation in RNA viruses. RNA polymerase is a low-fidelity transcription enzyme without a proofreading function. The high rate of replication of these viruses with low fidelity generates many new amino acid substitutions in surface glycoproteins, some of which will be advantageous to the virus, allowing it to

become an epidemic strain. Studies have shown that from 1968 to 1979, 7.9 nucleotide and 3.4 amino acid changes occurred per year, equivalent to an approximate annual 1% change in the amino acid composition of the HA. High rates of antigenic change are observed in the five specific epitopes of HA that surround the binding site; as noted previously, the binding site itself demonstrates little sequence variation. It is assumed that antibody to these epitopes sterically block access to the specific binding site, preventing attachment to and infection of host cells. Amino acid sequencing has shown that drift variants are sequential, suggesting selective pressure. For example, H3 sequential drift variants from 1968 to 1988 had four or more amino acid differences in at least two antigenic sites. The 1930s H1N1 virus strain (which was the first cultured influenza) shows substantial genetic drift from the ancestral 1918 H1N1 pandemic strain. It is also possible that changes in nonsurface proteins may influence replication, transmission, or tissue tropism (virulence), conferring a selective advantage to a specific strain. It is thought that after 10 to 30 years of circulation of a specific subtype most members of the population will have antibody to that subtype, increasing the selection pressure for a new shift variant.

Antigenic shift describes the major changes of HA, NA, or both of these surface antigens that create a new subtype. If the HA and NA determinants are novel, no antibody protection is present in human populations, and the stage may be set for a pandemic.

Viruses with segmented genomes can generate new variants rapidly by the random reassortment of the RNA segments. Coinfection of a single host cell by two influenza strains, each with a different eight-segmented genome, theoretically can generate 2^8 or 254 variants. It is thought that the "mixing vessel" host for influenza is likely swine, which are in contact with birds and humans, although humans can also serve this role. Most new variants do not have a survival advantage and die out. However, if a shift variant (1) retains the ability to replicate well in humans, (2) is efficiently transmissible between humans, and (3) has new surface HA or NA determinants that evade existing influenza antibody profiles in the human population, a pandemic may ensue. Historically, serology and virology reveal that three antigenic shifts occurred during the 20th century, leading to three pandemics. Table 15-2 summarizes antigenic shifts of influenza A virus over the last century. Figure 15-2 demonstrates details of the antigenic shift of 1968, and Figure 15-3 shows all pandemics.

Four pandemics have occurred in the 20th century: in 1918, the pandemic of influenza A H1N1 Spanish flu killed at least 50 million people in the first year; 500,000 died in the United States alone. In 1957, a major shift occurred with both new avian HA and NA (H1N1 to H2N2). In 1968, a new HA (H2N2 to H3N2) from an avian source was introduced, leading to a moderately severe pandemic. In 1977, the old 1951 H1N1 strain reappeared (likely having escaped from a laboratory), causing attack rates of more than 50% in younger members of the population who had been born after 1956 and, therefore, had no antibody to the earlier H1N1 subtype present from 1918 to 1957. Since 1977, both H1N1 and H3N2 subtypes cocirculate worldwide (Figure 15-2 and Figure 15-3).

To summarize, influenza viruses with new surface antigens emerge, cause a pandemic, and become established in human populations. As the proportion

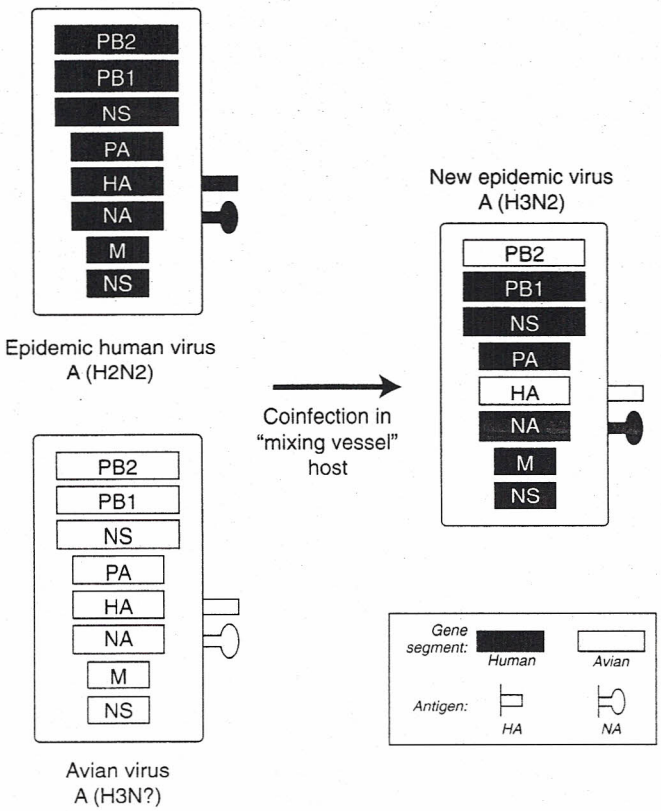
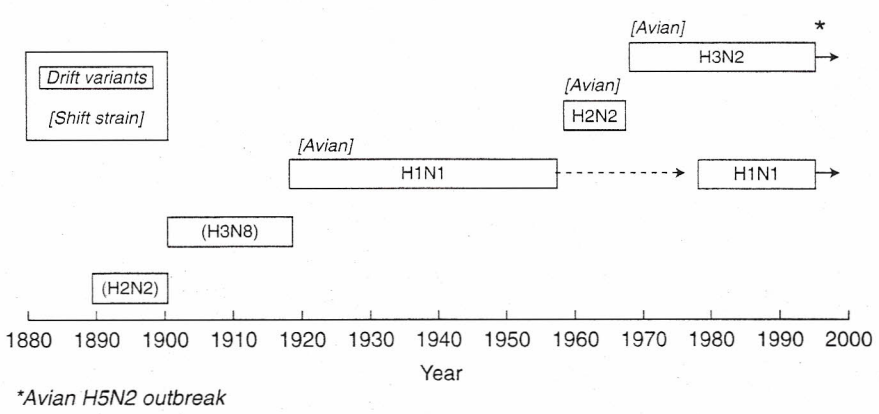


FIGURE 15-2 Diagram showing the last antigenic shift in 1968, when a new avian gene was acquired. Gene segments represent avian or human species origin and their associated surface proteins.
Source: Copyright © Mark C. Steinhoff.



**Avian H5N2 outbreak*

FIGURE 15-3 Twentieth-century history of influenza antigenic shifts and pandemics, and interpandemic antigenic drift.
Source: Centers for Disease Control and Prevention.

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BOX 15-1 1918 Pandemic Flu

The influenza pandemic of 1918–1919, referred to as the "Spanish flu," caused more deaths globally than any pandemic since the Black Death (bubonic plague) of the 14th century. Estimates of the total number of deaths worldwide vary, but most sources estimate the pandemic caused at least 20 to 50 million deaths in the first 12 months. This estimate is an obvious underestimate because deaths in Asia and Africa were crudely estimated by colonial authorities.

First Wave

It appears influenza illness was first reported among American troops in the midwestern United States, from where it seems to have spread across the Atlantic with the movement of 1.5 million US forces to the Western front. Influenza was reported in March 1918 from Ft. Riley, Kansas. In April, relatively mild influenza disease with low mortality was reported in troops on the East Coast. By the 15th of April, US troops in France were reporting influenza illnesses, as were troops in Britain. It is likely that crowding increased attack rates and mortality in the military; the U.S. Navy estimated that 40% of its seamen became ill. There were 54,000 battle deaths among US forces in Europe and 43,000 influenza and pneumonia deaths. Battle lines were no barrier; German troops reported *blitzkatarrh* shortly after US troops reported influenza, and German commanders complained that the disease disrupted their attack plans. By May and June 1918, most of Europe was experiencing the epidemic. Disease was reported in Africa in May, in India and China in July and August—influenza had circled the world in 5 months. During the summer, the character of the disease changed, showing higher rates of pneumonia in young adults with case fatality rates of 50%. Some authorities suggest that the virus had mutated into a more virulent form. Isolated island populations suffered greatly. For example, in Tahiti 10% of the population died within 25 days of the onset of the epidemic. Similarly, in Western Samoa in November 1918, 20% of the population of 38,000 died within a 2-month period. On the other hand, the Tristan da Cunha islands, isolated in the South Atlantic, did not experience the pandemic.

Second Wave

Beginning in August 1918, a second wave of severe disease which was called "Spanish flu" swept the East Coast of the United States, following the European outbreaks. (Because of wartime censorship, British, French, German, and US authorities did not report epidemic disease; Spain was neutral, reported the epidemic, and hence was awarded the name.) This time the United States experienced the severe influenza disease with higher case fatality rates seen in the European Western Front. A common description is of cyanosis and death from pneumonia within 2 to 3 days of illness onset. Surveys in the United States showed that 280/1000 persons had clinical influenza symptoms. An estimated 550,000 excess deaths occurred in the United States, meaning approximately 1 of 200 persons died of influenza during the winter of 1918–1919. Philadelphia reported the highest mortality rate: 12,897 influenza

and pneumonia deaths in October and November of 1918, with a peak of 700 deaths/day in late October, a 2-month mortality rate of 0.77%, leading to disruption of civic life, including a shortage of coffins. Desperate medical and public health authorities recommended many remedies and preventive actions now regarded as ineffective, including the use of gauze face masks, aerosol sprays, garlic or camphor necklaces, and legislation against public spitting. Mortality rates were lower in military and civilian African-Americans than in whites, but approximately 2% of all Native Americans died during the epidemic. The Spanish influenza epidemic of 1918 has been substantially ignored by historians until recently, perhaps because it occurred at the end of World War I. Katherine Anne Porter's novel, *Pale Horse, Pale Rider*, describes the experiences of young Americans during the pandemic.

1976 Swine Flu

When in January 1976 a similar swine H1N1 strain (A/New Jersey/76) was isolated in an ill soldier who died at Fort Dix, New Jersey, some United States public health authorities feared another pandemic and advised expanded immunization. Although not supported by all experts, a decision was reached to initiate mass immunization against swine flu, and the Swine Flu Program was announced in March 1976. A new national surveillance program for influenza disease and for vaccine adverse events was implemented. When liability issues were raised by the manufacturers, a special Swine Flu Tort Claims bill was passed by Congress, which specified that any claim arising from the swine flu program should be filed against the federal government. Vaccination started in October 1976, although no cases of swine flu disease had been reported. When, in December 1976, hundreds of cases of Guillain-Barré disease were reported following swine flu immunization, the vaccination program was suspended.[36]

The two major architects of the program, the Director of the CDC and the Assistant Secretary for Health of HEW, resigned. A total of 48 million Americans received the swine flu vaccine, but only six cases of swine flu H1N1 disease were recorded, which suggests that the A/New Jersey/76 strain was not transmitted efficiently. More than 500 cases of Guillain-Barré syndrome were reported, apparently associated with influenza vaccine, for which the federal government assumed liability and paid damages. Analysis suggested the risk of Guillain-Barré syndrome in 1976 vaccinees was 7 to 10 times increased over background risk, to about 10 cases for every million vaccine recipients. A recent evaluation of Guillain-Barré syndrome associated with current influenza vaccine suggests a relative risk of 1.7, approximately 1 case per million vaccinees.[37] This suggests the 1976 H1N1 vaccine had a unique association with Guillain-Barré syndrome.

1918 Virus Resurrected

The 1918 pandemic virus was unique in its disease syndrome and epidemiology, but it was not available for study as virology techniques did not exist at that time. In late 2005, the 1918 pandemic virus was re-created from viral RNA from a victim buried in permafrost and from autopsy material from

two soldiers. Genomic viral RNA was obtained from these three sources and sequenced to generate a complete 1918 genomic sequence. These sequences show the avian heritage of the virus. Using plasmid-mediated reverse genetics, the 1918 pandemic virus was generated and studied in a high-containment laboratory. In comparison to current epidemic H1N1 viruses, the 1918 virus displayed high growth characteristics in human bronchial epithelial cells in culture. It caused death in 100% of mice within 4 days, whereas the control viruses killed none. In summary, the biologic tour de force of resurrecting the 1918 virus will allow detailed assessment of the molecular basis of its high pathogenicity and unique transmission patterns.[12a, 14-16]

of persons with antibodies against the specific pandemic strain increases within the population, the circulating influenza virus subtype must change or die out. Antigenic drift allows a specific influenza subtype to persist in the human population. It is assumed that annual epidemics occur in the interpandemic period because drift variant viruses with new minor antigenic changes can infect some members of the population.

A new pandemic occurs after an antigenic shift. The shift can result from genetic reassortment between human and animal influenza viruses or from direct transmission of an animal strain to humans, as was documented with influenza A (H5N1) in Hong Kong in the winter of 1997–1998 and again in Southeast Asia in 2002–2004.[13] This virus when isolated from humans had only avian genes, with no evidence of reassortment with human viruses. It is apparent that the novel avian influenza A (H5N1) virus did cause disease in at least 18 humans in Hong Kong (6 of whom died), but did not efficiently transmit from human to human, hence did not become pandemic. H5N1 has reappeared in humans in 2003 in Hong Kong, and in 2004–2005 in Vietnam, Thailand, Cambodia, and Indonesia with evidence of rapid mutation.[10] This avian virus may at any time reassort with human-adapted viruses and acquire efficient transmissibility and could cause a pandemic in the near future. For this reason, public health authorities have begun development of H5 vaccines. H9N2 avian strains caused mild disease in Hong Kong in 1999 and 2003. Avian H7N7 caused poultry and human illness in Netherlands in 2003.[10]

The 1998 Hong Kong experience and the 1976 swine influenza episode show that surface antigens, virulence, and transmissibility all vary independently and unpredictably. Not all new shift viruses with novel antigens will cause a pandemic; the criteria of transmissibility and human infectivity must also be met.

Genetic reassortment also occurs frequently in egg or tissue culture. The vaccine manufacturers use this viral characteristic to rapidly develop new vaccine strains. Two viruses are selected: a wild virus with the epidemic NA and HA antigens, and an egg-adapted virus (A/Puerto Rico/8/34) with the characteristics of vigorous growth in egg culture. Eggs are infected simultaneously with both viruses and the reassortant progeny virus that exhibits both the epidemic HA and NA and the property of good growth in eggs is selected as the vaccine strain for production.

Epizootic Infections and Evolutionary History

The current working hypothesis developed by Webster and others is that avian influenza strains are the source for all influenza viruses seen in birds and mammals.[11-13] Analysis of molecular relationships suggests that all A subtypes are descended from a primordial avian influenza virus. All the known 15 HA and 9 NA influenza subtypes have been isolated from aquatic avian sources, which is likely their natural habitat, but only certain subtypes are found in mammalian species including swine, horses, seals, whales, and mink. Infection of feral (ducks, geese, gulls, terns, and shearwaters) or domestic (turkeys, chickens, geese, ducks, quail, and pheasants) avian species is usually asymptomatic, but occasionally has resulted in epidemics of avian disease, or "fowl plague." Ducks excrete up to $10^{8.7}$ virus particles per gram of feces, and influenza virus is found in waters where ducks reside. The rate of antigenic drift is low in birds, suggesting stable adaptation between virus and avian host. It has been found that pigs have epithelial cell receptors for both human and avian HA. Pigs are thought to be the mixing vessels or intermediate hosts of avian and mammalian influenza virus, providing an opportunity for reassortment and antigenic shift.

Although the virus of the 1918 pandemic has not been cultured, pandemic H1N1 viral RNA from bodies buried in permafrost in Alaska and from WWI autopsy material from the military has been analyzed and shows that the pandemic strain was unique and related to avian strains. Further analysis of the RNA sequence is being carried out to determine if a genetic explanation for its high virulence can be obtained.[14-16] It is of note that the avian equivalent of H1N1 is still circulating in avian species. The role of avian carriage of virus during annual waterfowl migration from the Northern to the Southern Hemisphere in the spread of new influenza variants is being investigated.

Prevention Strategies and Treatment

Vaccines to prevent infection and use of antiviral drugs either prophylactically or for treatment are the currently available strategies to reduce influenza disease. This section will describe the recommended use of inactivated and live attenuated influenza vaccines, and of antiviral drugs.

Vaccines

Vaccines were developed soon after influenza virus was shown to grow in embryonated hens' eggs. An early vaccine trial in 1943 showed that a killed virus vaccine was effective in young adults. The current inactivated vaccine is derived from virus grown on chorioallantoic membranes of embryonated eggs. The allantoic fluids are ultracentrifuged to purify the virus particles, and the viruses are inactivated by formaldehyde or beta-propriolactone. Some manufacturers disrupt the virus particles to produce a "split virus vaccine" using detergents or ether. The potency is assessed by measuring HA antigen, and vaccines are standardized to contain 15 to 20 μg of HA antigen per dose. Egg-grown influenza viruses have been shown to have antigenic

variation from the parent human strain, which may account for the variable protection of inactivated vaccines. Some workers have shown that growth of human-derived influenza virus in human cell lines produces HA antigens with identical amino acid sequences to the parent strain. In general, vaccines are immunogenic in adults after a single dose, but require two doses in infants and children who are immunologically naive. Current inactivated vaccines are 50% to 80% effective in preventing disease when the epidemic influenza virus matches the vaccine strains.[17]

The current vaccine strategy in the United States has evolved from protection for persons at high risk for adverse outcomes from influenza virus infection,[17a,17b] to now also vaccinating healthy persons who may transmit virus to high-risk persons.[18–22] In brief, these groups include those at increased risk for influenza complications (see Table 15-4), persons who can transmit influenza to those at high risk, as well as other special groups including persons infected with HIV,[23] travelers, and members of the population who wish to avoid influenza infection. Cost-effectiveness analyses mostly support immunization of healthy subjects.[20,21] Table 15-4 summarizes 2004 influenza vaccine recommendations for the United States (see CDC Web site for updates). Over the past few years infants and others have been added to the high-risk group.[24–26] Pregnancy was associated with excess mortality in the 1918 influenza pandemic. Recent evaluations have shown a relative risk of 4.7 for influenza-related hospitalization of pregnant women in the third trimester, compared with postpartum controls.[27]

Virus mutability with antigenic shift and drift means a new vaccine must be produced each year to counter the new antigenic variants that continually arise. Each year in January a review of circulating viruses in the Northern and Southern Hemispheres is undertaken by WHO, using data from a global network of surveillance laboratories, and the most likely epidemic influenza A (H1N1, H3N2) and a B strain are selected. The vaccine seed viruses are produced and distributed to manufacturers for production in eggs, clinical testing, licensing,[28,29] packaging, and distribution by October before the winter influenza season. The US vaccine manufacturers produce up to 100 million doses each year between February and October. Globally, nine manufacturers produce about 250 million doses annually.[30,31] This complex process is repeated annually and is usually effective, though in some years manufacturing problems have lead to late or nondelivery of vaccine.[56]

Usually this vaccine strategy is relatively effective in preventing disease and mortality in vaccinated persons in those years in which the vaccine composition closely matches the epidemic virus. It is unlikely to have any impact on the overall epidemic pattern, however, because only a small proportion of the susceptible population (i.e., those at high risk) is vaccinated. Recent studies suggest that influenza immunization of healthy children will reduce all otitis media episodes by 40%, and immunization of day-care children reduces illness in their families.[33–34] Immunization of healthy adults will reduce reported respiratory illness by 20% and absenteeism by 36%.[20] The vaccine strategy to vaccinate healthy persons, especially children, is increasingly used and had been used in Japan until the early 1990s.[32] Strategies to vaccinate a proportion of the children have the potential to disrupt epidemic transmission and protect adults.[35]

The inactivated influenza vaccines that are currently recommended and commercially available do not contain live viruses and cannot cause influenza

TABLE 15-4 Target Groups for Vaccination, CDC/ACIP 2005–2006 (see www.CDC.GOV/flu for latest recommendations)

A. Persons at Increased Risk for Complications

Vaccination with inactivated influenza vaccine is recommended for the following persons who are at increased risk for complications from influenza:

- Persons aged ≥65 years;
- Residents of nursing homes and other chronic-care facilities that house persons of any age who have chronic medical conditions;
- Adults and children who have chronic disorders of the pulmonary or cardiovascular systems, including asthma (hypertension is not considered a high-risk condition);
- Adults and children who have required regular medical follow-up or hospitalization during the preceding year because of chronic metabolic diseases (including diabetes mellitus), renal dysfunction, hemoglobinopathies, or immunosuppression (including immunosuppression caused by medications or by human immunodeficiency virus [HIV]);
- Adults and children who have any condition (e.g., cognitive dysfunction, spinal cord injuries, seizure disorders, or other neuromuscular disorders) that can compromise respiratory function or the handling of respiratory secretions or that can increase the risk for aspiration;
- Children and adolescents (aged 6 months–18 years) who are receiving long-term aspirin therapy and, therefore, might be at risk for experiencing Reye syndrome after influenza infection;
- Women who will be pregnant during the influenza season; and
- Children aged 6–23 months.

B. Persons Aged 50–64 Years

C. Persons Who Can Transmit Influenza to Those at High Risk

- Employees of assisted living and other residences for persons in groups at high risk;
- Persons who provide home care to persons in groups at high risk; and
- Household contacts (including children) of persons in groups at high risk.

D. Health-Care Workers

E. Pregnant Women

Because of the increased risk for influenza-related complications, women who will be pregnant during the influenza season should be vaccinated. Vaccination can occur in any trimester.

F. Persons Infected with HIV

Because influenza can result in serious illness and because vaccination with inactivated influenza vaccine can result in the production of protective antibody titers, vaccination will benefit HIV-infected persons, including HIV-infected pregnant women.

G. Breastfeeding Mothers, to Protect Young Infants

H. Travelers

- Travel to the tropics,
- Travel with organized tourist groups at any time of year, or
- Travel to the Southern Hemisphere during April–September.

I. General Population

Physicians should administer influenza vaccine to any person who wishes to reduce the likelihood of becoming ill with influenza or transmitting influenza to others should they become infected.

Source: Centers for Disease Control and Prevention.[17,17a,17b,17c]

disease. The most frequent side effect of vaccination is local soreness at the vaccination site, which can last for 1 or 2 days. Symptoms of fever, malaise, and myalgia have been infrequently reported, most often in persons who have had no exposure to influenza vaccine (e.g., young children). Allergic anaphylactic reactions, which can occur rarely after influenza vaccination, are related to hypersensitivity to residual egg protein in these vaccines or to thimerosal. The 1976 swine influenza vaccine was associated with an increased frequency of Guillain-Barré syndrome of ascending paralysis.[36] Recently, the association has been evaluated with current vaccines, and it is estimated to occur in approximately one case per million vaccinees—far less than the risk of severe influenza complications if not vaccinated.[37]

Live Influenza Vaccine

Live attenuated influenza viruses (LAIV) have been shown to be as effective as the inactivated virus vaccines.[19,20] The cold-adapted virus does not replicate effectively at 37°C, hence it can infect humans, but does not cause disease.[38] The cold-adapted attenuated influenza virus is derived from an epidemic strain and an attenuated cold-adapted virus. After reassortment of the two viruses, progeny with the epidemic surface antigens and the characteristic of attenuated growth in humans are selected and produced. These vaccine strains have been extensively tested in adults and children, and demonstrate protective efficacy of 92% against confirmed influenza infection and excellent safety characteristics.[19,39,40] Their chief advantage is that they can be administered as nose drops or aerosol, and, therefore, are more acceptable to patients and do not require medical personnel for administration. The cold-adapted influenza vaccine (FluMist®) was licensed in 2004 for use in people aged 5 years to 55 years in the United States with important exceptions (Table 15-5).[41] The ease of administration of LAIV vaccines and their ready acceptance may allow strategies of population vaccination to avert an epidemic.

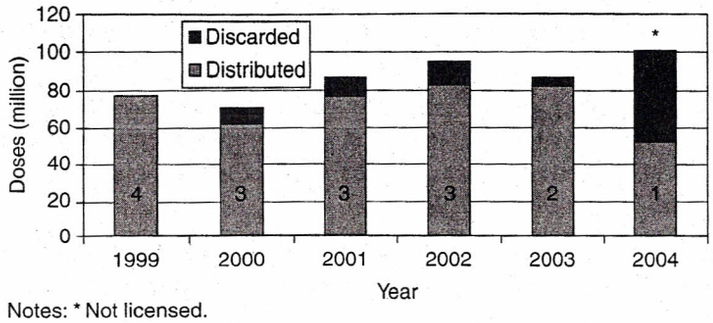
Vaccine Production Issues

Production of influenza vaccine is a complex process nearly 50 years old that involves production, licensing, and delivery of a trivalent vaccine every

TABLE 15-5 Persons Who Should Not Be Vaccinated with LAIV

The following populations should not be vaccinated with LAIV:

- Persons younger than 5 years or those *older than* 50 years
- Persons with asthma, reactive airways disease, or other chronic disorders of the pulmonary or cardiovascular systems; persons with other underlying medical conditions, including such metabolic diseases as diabetes, renal dysfunction, and hemoglobinopathies; or persons with known or suspected immunodeficiency diseases or who are receiving immunosuppressive therapies
- Children or adolescents receiving aspirin or other salicylates (because of the association of Reye syndrome with wild-type influenza infection)
- Persons with a history of GBS
- Pregnant women
- Persons with a history of hypersensitivity, including anaphylaxis, to any of the components of LAIV or to eggs



Notes: * Not licensed.

FIGURE 15-4 Influenza vaccine doses.
Source: Data from Centers for Disease Control and Prevention, Figure © Mark C. Steinhoff.

year. The current licensed vaccines are made in embryonated hens' eggs, and approximately 80 to 100 million doses are produced in the United States each year requiring 300 million eggs. Because of increased information regarding high-risk groups, policy decisions have gradually increased the number of people who are recommended to receive the vaccine annually. In 1997, pregnant women were added, persons aged 50 to 64 were added in 2000, and young children from 6 to 24 months were added in 2004[40a] bringing the total number to 180 million. At the same time, the number of vaccine producers in the United States declined from four to two. Figure 15-4 shows the total production of doses each year and the number of doses discarded unsold at the end of the season. In 2004, there were only two producers who between them produced a 100 million doses. However, one of the producers was not able to distribute approximately 48 million doses because of production problems and withdrawal of its license by FDA. The resulting shortfall of vaccine required revision of priority groups for immunization by authorities and redistribution of vaccine doses, as well as importation of vaccine as investigational drugs from producers who are not licensed in the United States.

The combination of complex manufacture process, reduction of producers, and the complexities of annual vaccine production conspired to produce a disruption of the vaccine supply. These events and increased concern about new pandemic strains prompted the US government in 2005 to a series of actions including (1) funding support to maintain the chicken flocks so that large numbers of embryonated eggs can be made available for vaccine production with a short lead time. In addition, (2) encouragement of new manufacturers to apply for US licensure to increase vaccine production sources, and (3) initiation of the process to produce influenza vaccine from cell culture rather than from hens' eggs.

Antiviral Drugs

The older antiviral agents, amantadine and rimantadine, inhibit the replication of type A influenza viruses (but have no effect on type B) by interfering with the M2 protein, which forms an ion channel. When taken prophylactically, these drugs have been shown to be 70% to 90% effective in preventing illness during influenza A epidemics. In addition, if begun within 48

TABLE 15-6 Antiviral Agents for Influenza Treatment and Prophylaxis

	Amantadine	Rimantadine	Zanamivir	Oseltamivir
Types of influenza viruses inhibited	Influenza A	Influenza A	Influenza A and B	Influenza A and B
Route of administration	Oral (tablet, capsule, syrup)	Oral (tablet, syrup)	Oral inhalation*	Oral (capsule)
Ages for which treatment is approved	≥1 year	≥14 years	≥1 year	≥1 year
Ages for which prophylaxis is approved	≥1 year	≥1 year	Not approved for prophylaxis	≥1 year

*Zanamivir is administered by a plastic oral inhalation device.
Source: Adapted from MMWR, Vol. 48, RR14, 1999, Centers for Disease Control and Prevention.

hours of illness onset in healthy adults, these drugs can reduce the severity and duration of influenza A illness. Both drugs have CNS side effects of nervousness, anxiety, difficulty in concentrating, and light-headedness. These drugs are advised for children only above the age of 1 year (Table 15-6) and are not effective against H_5N_1.[41,42]

New drugs have been designed to inhibit NA activity.[43,44] An NA inhibitor, zanamivir (a sialic acid analogue), reduces disease duration by 1 or more days and prevents both type A and B disease with 67% to 82% effectiveness when taken prophylactically.[45] Zanamivir (or Relenza) was licensed in the United States in July 1999 as inhalation therapy for persons older than 7 years. An oral NA inhibitor, oseltamivir (Tamiflu), is equally effective for prophylaxis and treatment for influenza in children older than 1 year.[46]

Preparing for the Pandemic [as of June, 2006]

Many experts predict that a new pandemic with a unique influenza shift virus is inevitable. The ceaseless random variation of influenza virus will eventually result in the development of a pandemic strain.

The increasing cases of avian H5N1 virus in humans in Asia since 2003 has led to a reassessment of pandemic planning in the United States and globally.

Avian Influenza Virus

The H5N1 avian influenza strain has been causing disease and outbreaks in birds and humans in Asia since 1997. As of late May 2006, 225 human cases of laboratory-confirmed avian influenza A/H5N1 had been reported to WHO since 2003. The majority of cases were from Asia, including the countries of Cambodia, China, Indonesia, Thailand and Vietnam; with fewer cases from Africa in Egypt, and Djibouti, and several cases from Europe and the Middle East, in Iraq, Turkey and Azerbijan. Overall mortality in these reported cases was 57%. Analysis of recent strains of H5N1 show that it has mutated substantially from the strain first seen in 1997.[47,47A] There is increasing concern regarding this avian virus that exhibits new surface antigen, has virulence in humans, but does not yet have efficient transmissibility between humans.[47b,47c]

The virus may acquire the human transmission phenotype properties needed to become the next pandemic strain.[9]

In its review of preparedness, the CDC has estimated that a new virus would arrive in the United States within 1 to 6 months of its appearance elsewhere, and would likely initiate the pandemic at many cities with international airports. It is unlikely that any existing vaccine would be useful, and stocks of antivirals would not be adequate to treat the large number of cases expected in a naive population. As in previous pandemics, health care workers will likely be at increased risk of illness, affecting the care of the ill. Current estimates are that the United States would have 200 million cases, up to 800,000 hospitalizations, and as many as 300,000 influenza deaths within the 3- to 4-month period of the first sweep of the pandemic. (See www.cdc.gov/vd/nvpo/pandemicflu.htm for the current planning guide.) Current plans include improved surveillance and monitoring of the emergence of new viruses,[48] stockpiling of antiviral drugs,[49] development of a drug distribution system, strategic planning to develop and distribute new vaccines, and improved communications between WHO and national and local authorities.[50,51,51a] Priority groups to receive vaccine and hospital care have been described and debated.[51b–51f]

The WHO has strengthened the FluNet, a global surveillance system with laboratories in 83 countries and has sped up the process of identifying possible new shift viruses (those that are not typed with existing antisera). The FluNet showed its effectiveness in identifying the new coronavirus agent of SARS, not influenza, as the cause of an outbreak of severe febrile respiratory illness in Hong Kong in 2003. FluNet was used to rapidly identify human cases of avian influenza in 1997. Some experts have suggested that closer monitoring of avian and swine influenza viruses and epidemic diseases may assist in prediction of new pandemic human influenza strains.[52] Virologists are working on techniques to adapt a newly arising influenza virus for rapid production of a vaccine.[53] Because the onset of a new pandemic or the characteristics of a new pandemic virus cannot be predicted reliably, preparation to speed the response to the pandemic may be the best approach.[54,55]

If a pandemic should occur before sufficient antiviral drugs are available, and few or no doses of specific vaccines are available,[56,56a] epidemic control will have to rely on public health strategies that are centuries old, namely physical restrictions of citizens. This includes (1) isolation of those with influenza illness, (2) quarantine of all their contacts, and (3) banning of all public gatherings including schools, workplaces, shopping centers, churches, and bars. A presidential executive order was signed on April 2, 2004, permitting the use of quarantine if an avian influenza outbreak should occur.

References

1. Smith W, Andrews CH, Laidlaw PP. A virus isolated from influenza patients. *Lancet.* 1933;2:66–68.
2. Murphy BR, Webster RG. "Orthomyxovirus." In: Fields BN, Knipe DM, Howley PM, et al., eds. *Virology.* 3rd ed. Philadelphia, Pa: Lippincott-Raven Publishers; 1996:1409–1432.
3. Matrosovich MN, Gambaryan AS, Teneberg S, et al. Avian influenza A viruses differ from human viruses by recognition of

sialyloligosaccharides and gangliosides and by a higher conservation of the HA receptor-binding site. *Virology.* 1997;233:224–234.

3a. Brundage JF. Interactions between influenza and bacterial respiratory pathogens: implications for pandemic preparedness. *Lancet Infect Dis.* 2006;6:303–312.

3b. O'Brien KL, Walters MI, Sellman J, Quinlisk P, Regnery H, Schwartz B, Dowell SF. Severe pneumococcal pneumonia in previously healthy children: the role of preceding influenza infections. *Clin Infect Dis.* 2000;30:784–789.

4. Monto AS, Gravenstein S, Elliott M, Colopy M, Schweinle J. Clinical signs and symptoms predicting influenza infection. *Arch Intern Med.* 2000;160:3243–3247.

5. Couch RB, Kasel WP, Glezen TR, et al. Influenza: its control and person and populations. *J Infect Dis.* 1986;153:431–440.

6. Rao BL, Banerjee K. Influenza surveillance in Pune, India, 1978–90. *Bull World Health Organ.* 1993.

6a. Viboud C, Alonso WJ, Simonsen L. Influenza in tropical regions. PLoS Medicine Vol. 3 , No. 4, DOI: 10.1371/journal.pmed.0030089.

6b. Chiu SS, Lau YL, Chan KH, Wong WHS, Peiris JSM. Influenza-related hospitalizations among children in Hong Kong. *N Engl J Med.* 2002;347:2097–2103.

6c. Neuzil KM, Zhu Y, Griffin MR, et al. Burden of interpandemic influenza in children young than 5 years: a 25 year prospective study. *J Infect Dis.* 2002;185:147–152.

6d. Bhat N, Wright JG, Broder KR, et al. Influenza-associated deaths among children in the United States, 2003–2004. *N Engl J Med.* 2005;353(24):2559–2567.

7. Reichert TA, Simonsen L, Sharma A, Pardo SA, Fedson DS, Miller MA. Influenza and the winter increase in mortality in the United States, 1959–1999. *Am J Epidemiol.* 2004;160:492–502.

7a. Thompson WW, Shay DK, Weintraub E, Brammer L, Bridges CB, Cox NJ, Fukuda K. Influenza-associated hospitalizations in the United States. *JAMA.* 2004 15;292(11):1333–1340.

8. Subbarao K, Klimov A, Katz J, et al. Characterization of an avian influenza A (H5N1) virus isolated from a child with fatal respiratory illness. *Science.* 1998;279:393–396.

9. Stöhr K. Avian influenza and pandemics—research needs and opportunities. *N Engl J Med.* 2005;352;405–407.

10. Koopmans M, Wilbrink B, Conyn M, et al. Transmission of H7N7 avian influenza A virus to human beings during a large outbreak in commercial poultry farms in the Netherlands. *Lancet.* 2004;363: 587–593.

11. Webster RG. Influenza: an emerging microbial pathogen. In: Krause RM, ed. *Emerging Infections.* New York, NY: Academic Press; 1998:275–300.

12. Hay AJ, Gregory V, Douglas AR, Lin YP. The evolution of human influenza viruses. *Phil Trans R Soc Lond B.* 2001;356:1861–1870.

12a. Tumpey TM, Garcia-Sastre A, Taubenberger, et al. Pathogenicity of influenza viruses with genes from the 1918 pandemic virus: functional roles of alveolar macrophages and neutrophils in limiting virus replication and mortality in mice. *J Virol.* 2005;79(23):14933–14944.

13. Webby R, Hoffmann E, Webster R. Molecular constraints to interspecies transmission of viral pathogens. *Nature Med.* 2004;10: S77-S81.

14. Reid AH, Fanning TG, Hultin JV, Taubenberger JK. Origin and evolution of the 1918 "Spanish" influenza virus hemagglutinin gene [comment]. *Proc Natl Acad Sci U S A.* 1999;96:1164–1166.
15. Tumpey TM, Basler CF, Aguilar PV, et al. Characterization of the reconstructed 1918 Spanish influenza pandemic virus. *Science.* 2005;310:77–80.
16. Taubenberger JK, Reid AH, Lourens RM, et al. Characterization of the 1918 influenza virus polymerase genes [letter]. *Nature.* 2005;437: 889–892.
17. Recommendations of the Advisory Committee on Immunization Practices (ACIP). Prevention and Control of Influenza. *MMWR.* 2005;54(RR08):1–40.
17a. Recommendations of the Healthcare Infection Control Practices Advisory Committee (HICPAC) and the Advisory Committee on Immunization Practices (ACIP). Influenza Vaccination of Health-Care Personnel. *MMWR.* 2006;55(RR02);1–16.
17b. Poland GA, Tosh P, Jacobson RM. Requiring influenza vaccination for health care workers: seven truths we must accept. *Vaccine.* 2005;23(17–18):2251–2255.
17c. American Academy of Pediatrics. Influenza. In: Pickering LK, Baker CJ, Long SS, McMillan JA, eds. *Red Book: 2006 Report of the Committee on Infectious Diseases.* 27th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2006:401–410.
18. Nichol KL, Lind A, Margolis KL, et al. The effectiveness of vaccination against influenza in healthy, working adults. *N Engl J Med.* 1995;333:889–893.
19. Nichol KL, Mendelman PM, Mallon KP, et al. Effectiveness of live, attenuated intranasal influenza virus vaccine in healthy, working adults. A randomized controlled trial. *JAMA.* 1999;282:137–144.
20. Nichol KL. The efficacy, effectiveness and cost-effectiveness of inactivated influenza virus vaccines. *Vaccine.* 2003;21:1769–1775.
21. Bridges CB, Thompson WW, Meltzer MI, et al. Effectiveness and cost-benefit of influenza vaccination of healthy working adults. *JAMA.* 2000;284:1655–1663.
22. Wilde JA, McMillan J, Serwint J, Butta J, O'Riordan MA, Steinhoff MC. Effectiveness of influenza vaccine in health care professionals: a randomized controlled trial. *JAMA.* 1999;281:908–913.
23. Tasker SA, Treanor JJ, Paxton WB, Wallace MR. Efficacy of influenza vaccination in HIV-infected persons. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med.* 1999;131:430–433.
24. Hurwitz ES, Haber M, Chang A, et al. Effectiveness of influenza vaccination of day care children in reducing influenza-related morbidity among household contacts. *JAMA.* 2000;284:1677–1682.
25. Izurieta HS, Thompson WW, Kramarz P, et al. Influenza and the rates of hospitalization for respiratory disease among infants and young children. *N Engl J Med.* 2000;232:232–239.
26. Neuzil KM, Mellen BG, Wright PF, Mitchel EF, Griffin MR. The effect of influenza on hospitalizations, outpatient visits, and courses of antibiotics in children. *N Engl J Med.* 2000;342:225–231.
27. Neuzil KM, Reed GW, Mitchel EF, Simonsen L, Griffin MR. Impact of influenza on acute cardiopulmonary hospitalizations in pregnant women. *Am J Epidemiol.* 1998;148:1094–1102.
28. Gerdil C. The annual production cycle for influenza vaccine. *Vaccine.* 2003;21:1776–1779.

29. Wood JM, Levandowski RA. The influenza vaccine licensing process. *Vaccine.* 2003;21:1786–1788.
30. Fedson DS, Hirota Y, Shin H-K, et al. Influenza vaccination in 22 developed countries: an update to 1995. *Vaccine.* 1997;15:1506–1511.
31. van Essen GA, Palache AM, Forleo E, Fedson DS. Influenza vaccination in 2000: recommendations and vaccine use in 50 developed and rapidly developing countries. *Vaccine.* 2003;21:1780–1785.
32. Reichert TA, Sugaya, Fedson DS, Glezen WP, Simonsen L, Tashiro M. The Japanese experience with vaccinating school children against influenza. *N Engl J Med.* 2001;344:889–896.
33. Heikkinen T, Ruuskanen O, Waris M, Ziegler T, Arola M, Halonen P. Influenza vaccination in the prevention of acute otitis media in children. *Am J Dis Child.* 1991;145:445–448.
34. Clements DA, Langdon L, Bland C, Walter E. Influenza A vaccine decreases the incidence of otitis media in 6- to 30-month-old children in day care. *Arch Pediatr Adolesc Med.* 1995;1490:1113–1117.
35. Piedra PA, Gaglani MJ, Kozinetz CA, et al. Herd immunity in adults against influenza-related illnesses with use of the trivalent-live attenuated influenza vaccine (CAIV-T) in children. *Vaccine.* 2005;23:1540–1548.
36. Langmuir AD, Bregman DJ, Kurland LT, Nathanson N, Victor M. An epidemiologic and clinical evaluation of Guillain-Barré syndrome reported in association with the administration of swine influenza vaccines. *Am J Epidemiol.* 1984;119:841–879.
37. Lasky T, Terracciano GJ, Magder L, et al. The Guillain-Barré Syndrome and the 1992–1993 and 1993–1994 influenza vaccines. *N Engl J Med.* 1998;339:1797–1802.
38. Steinhoff MC, Halsey NA, Fries LF, et al. The A/Mallard/6750/78 avian-human, but not the A/Ann Arbor/6/60 cold-adapted, Influenza A/Kawasaki/86 (H1N1) reassortant virus vaccine retains partial virulence for infants and children. *J Infect Dis.* 1991;163:1023–1028.
39. Belshe RB, Mendelman PM, Treanor J, et al.The efficacy of live attenuated, cold-adapted, trivalent, intranasal influenza virus vaccine in children. *N Engl J Med.* 1998;338:1405–1412.
40. Belshe RB, Nichol KL, Black SB, et al. Safety, efficacy, and effectiveness of live, attenuated, cold-adapted influenza vaccine in an indicated population aged 5–49 years. *CID.* 2004;39:920–927.
40a. http://www.cdc.gov/flu/professionals/vaccination/pdf/targetpopchart.pdf accessed 16 June, 2006.
41. Cooper NJ, Sutton AJ, Abrams KR, Wailoo A, Turner D, Nicholson KG. Effectiveness of neuraminidase inhibitors in treatment and prevention of influenza A and B: systematic review and meta-analyses of randomised controlled trials. *BMJ.* 2003;326:1235.
42. American Academy of Pediatrics. In: Pickering LK, ed. *Red Book: 2003 Report of the Committee on Infectious Diseases.* 26th ed. Elk Grove Village, Ill: American Academy of Pediatrics; 2003.
43. Hayden FG, Osterhaus ADME, Treanor JJ, et al, for the GG167 Influenza Study Group. Efficacy and safety of the neuraminidase inhibitor zanamivir in the treatment of influenzavirus infections. *N Engl J Med.* 1997;337:874–880.
44. Monto AS, Robinson DP, Herlocher ML, Hinson JM Jr, Elliott MJ, Crisp A. Zanamivir in the prevention of influenza among healthy adults. A randomized controlled trial. *JAMA.* 1999;282:31–35.
45. Monto AS, Pichichero ME, Blanckenberg SJ, et al. Zanamivir prophylaxis: an effective strategy for the prevention of influenza types A and B within households. *J Infect Dis.* 2002;186:1582–1588.

46. Welliver R, Monto AS, Carewicz O, et al. Effectiveness of oseltamivir in preventing influenza in household contacts: a randomized controlled trial. *JAMA.* 2001;285:748–754.
47. Webby RJ, Webster RG. Are we ready for pandemic influenza? *Science.* 2003;302:1519–1522.
47a. Chen H, Deng G, Li Z, et al. The evolution of H5N1 influenza viruses in ducks in southern China. *PNAS.* 2004;101:10452–10457.
47b. Beigel JH, Farrar J, Han AM, et al, Writing Committee of the World Health Organization (WHO) Consultation on Human Influenza A/H5. Avian influenza A (H5N1) infection in humans. *N Engl J Med.* 2005;353:1374–1385.
47c. Peltola VT, Murti KG, McCullers JA. Influenza virus neuraminidase contributes to secondary bacterial pneumonia. *J Infect Dis.* 2005;192:249–257.
48. Stöhr K. Asian influenza and pandemics. *N Engl J M* ed. 2005;352:405–407.
49. Longini IM Jr, Halloran E, Nizam A, Yang Y. Containing pandemic influenza with antiviral agents. *Am J Epidemiol.* 2004;159:623–633.
50. Fedson DS. Preparing for pandemic vaccination: an international policy agenda for vaccine development. *J Public Health Policy.* 2005;26:4–29.
51. World Health Organization. Department of Communicable Disease. Surveillance and Response Global Influenza Programme. WHO checklist for influenza pandemic preparedness planning. *WHO/CDS/CSR/GIP/2005.4, WHO/CDS/CSR/GIP/2005.5.*
51a. Osterholm MT. Preparing for the next pandemic. *N Engl J Med.* 2005;352:1839–1842.
51b. Emanuel EJ, Wertheimer A. Public health. Who should get influenza vaccine when not all can? *Science.* 2006;312(5775):854–855.
51c. Centers for Disease Control and Prevention (CDC). Update: influenza vaccine supply and recommendations for prioritization during the 2005–06 influenza season. *MMWR Morb Mortal Wkly Rep.* 2005;54(34):850.
51d. Daniel J. Barnett, Ran D. Balicer, Daniel R. Lucey, George S. Everly Jr., Saad B. Omer, Mark C. Steinhoff, Itamar Grotto. A Systematic Analytic Approach to Pandemic Influenza Preparedness Planning. *PLoS Medicine.* 2005; 2:e359.
51e. Ferguson NM, Cummings DAT, Fraser C, Cajka JC, Cooley PC, Burke DS. Strategies for mitigating an influenza pandemic. Nature 2006;doi:10.1038/nature04795 http://www.nature.com/nature.
51f. World Health Organization Writing Group. Nonpharmaceutical interventions for pandemic influenza, international measures. Emerg Infect Dis 2006;12:81–87.
52. Lipatov AS, Govorkova EA, Webby RJ, et al. Influenza: emergence and control. *J Virol.* 2004;78:8951–8959.
53. Stephenson I, Nicholson KG, Wood JM, Zambon MC, Katz JM. Confronting the avian influenza threat: vaccine development for a potential pandemic. *Lancet Infect Dis.* 2004;4:499–509.
54. Ferguson NM, Cummings DAT, Cauchemez S, et al. Strategies for containing an emerging influenza pandemic in Southeast Asia. *Nature.* 2005;437:209–214.
55. Longini IM Jr, Nizam A, Xu S, et al. Containing pandemic influenza at the source. *Science.* 2005;309:1083–1087.
56. Sloan FA, Berman S, Rosenbaum S, Chalk RA, Griffin RB. The fragility of the U.S. vaccine supply. *N Engl J Med.* 2004;351:2443–2447.
56a. Treanor J. Weathering the influenza vaccine crisis. *N Engl J Med.* 2004;351:2037–2040.

Internet Resources

- CDC influenza Web site: http://www.cdc.gov/flu.
- WHO influenza Web site: http://who.int/emc/diseases/flu/index.html.
- Interactive maps of global flu data: http://oms/b3e/jussieu/fr/flunet.
- Weekly report, influenza summary update: http://www.cdc.gov/flu/weekly/
- US pandemic plan: http://www.hhs.gov/nvpo/pandemicplan/index.html.
- Good summaries and updates from Center for Infectious Disease Research and Policy: www.CIDRAP/imn.edu
- CDC's flu activity report: http://www.cdc.gov/flu/weekly/fluactivity.htm
- US Government pandemic flu web page: www.pandemicflu.gov
- Nature's avian flu mapping on Google Earth: http://www.nature.com/nature/googleearth/avianflu1.kml
- US HHS flu pandemic planning update March 2006: http://pandemicflu.gov/plan/pdf/panflu20060313.pdf
- US National Strategy Pandemic Influenza plan document, May 2006.
- Homeland Security Council: http://www.whitehouse.gov/homeland/nspi_implementation.
- W.H.O. New International Health regulations for influenza: http://www.who.int/gb/ebwha/pdf_files/WHA59/A59_47-en.pdf
- W H O influenza web site: http://www.who.int/csr/disease/influenza/en/
- WHO global influenza preparedness plan: http://www.who.int/csr/resources/publications/influenza/WHO_CDS_CSR_GIP_2005_5.pdf
- WHO avian influenza page: http://www.who.int/csr/disease/avian_influenza/en/
- Cumulative number of confirmed human cases of avian influenza a/(H5N1) reported to WHO: http://www.who.int/csr/disease/avian_influenza/country/cases_table_2006_06_06/en/print.html

Bibliography

Barry JM. *The Great Influenza: The Epic Story of the Deadliest Plague in History.* New York, NY: Viking; 2004.

Crosby AW. *America's Forgotten Pandemic: The Influenza of 1918.* New York, NY: Cambridge University Press; 1989.

Getz D. *Purple Death: The Mysterious Flu of 1918.* New York, NY: Henry Holt & Company; 2000.

Kolata G. *Flu: The Story of the Great Influenza Pandemic of 1918 and the Search for the Virus That Caused It.* New York, NY: Farrar, Straus and Giroux; 1999.

Neustadt RE, Fineberg HV. *The Swine Flu Affair: Decision-Making on a Slippery Disease.* Washington, DC: US Dept of Health, Education, and Welfare; 1978.