In 1968, an antigenic shift involving only the hemagglutinin occurred (H2N2 to H3N2); the subsequent pandemic was less severe than that of 1957. In 1977, an H1N1 virus emerged and caused a pandemic that primarily affected younger individuals (i.e., those born after 1957). As shown in Table 224-1, H1N1 viruses circulated from 1918 to 1956; thus, individuals born prior to 1957 would be expected to have some degree of immunity to H1N1 viruses. The pandemic of 2009–2010 was caused by an A/H1N1 virus against which little immunity was present in the general population, although approximately one-third of individuals born before 1950 had some apparent immunity to related H1N1 strains.

During most outbreaks of influenza A, a single subtype has circulated at a time. However, since 1977, H1N1 and H3N2 viruses have circulated simultaneously, resulting in outbreaks of varying severity. In some outbreaks, influenza B viruses have also circulated simultaneously with influenza A viruses. In 2009–2010, the pandemic A/H1N1 virus appeared to circulate nearly exclusively.

FEATURES OF PANDEMIC AND INTERPANDEMIC INFLUENZA A Pandemics provide the most dramatic evidence of the impact of influenza A. However, illnesses occurring between pandemics (interpandemic disease) also account for extensive mortality and morbidity, albeit over a longer period. In the United States, influenza was associated with an average of 23,000 excess deaths per season in 1976–2007 and with a maximum of 48,600 excess deaths during the 2003–2004 season.

Influenza A viruses that circulate between pandemics demonstrate antigenic drifts in the H antigen. These antigenic drifts result from point mutations in the RNA segment that codes for the hemagglutinin and occur most frequently in five hypervariable regions. Epidemiologically significant strains—that is, those with the potential to cause widespread outbreaks—exhibit changes in amino acids in at least two of the major antigenic sites in the hemagglutinin molecule. Because two point mutations are unlikely to occur simultaneously, it is believed that antigenic drifts result from point mutations occurring sequentially during the spread of virus from person to person. Antigenic drifts have been reported nearly annually since 1977 for H1N1 viruses and since 1968 for H3N2 viruses.

Interpandemic influenza A outbreaks usually begin abruptly, peak over a 2- to 3-week period, generally last for 2–3 months, and often subside almost as rapidly as they began. In contrast, pandemic influenza may begin with rapid transmission at multiple locations, have high attack rates, and extend beyond the usual seasonality, with multiple waves of attack before or after the main outbreak. In interpandemic outbreaks, the first indication of influenza activity is an increase in the number of children with febrile respiratory illnesses who present for medical attention. This increase is followed by increases in rates of influenza-like illnesses among adults and eventually by an increase in hospital admissions for patients with pneumonia, worsening of congestive heart failure, and exacerbations of chronic pulmonary disease. Rates of absence from work and school also rise at this time. An increase in the number of deaths caused by pneumonia and influenza is generally a late observation in an outbreak. Attack rates have been highly variable from outbreak to outbreak in interpandemic influenza but most commonly are in the range of 10–20% of the general population.

Although pandemic influenza may occur throughout the year, interpandemic influenza occurs almost exclusively during the winter months in the temperate zones of the Northern and Southern hemispheres. In those locations, it is highly unusual to detect influenza A virus at other times, although rises in serum antibody titer or even outbreaks have been noted rarely during warm-weather months. In contrast, influenza virus infections occur throughout the year in the tropics. Where or how influenza A viruses persist between outbreaks in temperate zones is unknown. It is possible that the viruses are maintained in the human population on a worldwide basis by person-to-person transmission and that large population clusters support a low level of interepidemic transmission. Alternatively, human strains may persist in animal reservoirs. Convincing evidence to support either explanation is not available. In the modern era, rapid transportation may contribute to the transmission of viruses among widespread geographic locales.

The factors that result in the inception and termination of outbreaks of influenza A are incompletely understood. A major determinant of the extent and severity of an outbreak is the level of immunity in the population at risk. With the emergence of an antigenically novel influenza virus to which little or no immunity is present in a community, extensive outbreaks may occur. When the absence of immunity is worldwide, epidemic disease may spread around the globe, resulting in a pandemic. Such pandemic waves can continue for several years, until immunity in the population reaches a high level. In the years following pandemic influenza, antigenic drifts among influenza viruses result in outbreaks of variable severity in populations with high levels of immunity to the pandemic strain that circulated earlier. This situation persists until another antigenically novel pandemic strain emerges. On the other hand, outbreaks sometimes end despite the persistence of a large pool of susceptible individuals in the population. It has been suggested that certain influenza A viruses may be intrinsically less virulent and cause less severe disease than other variants, even in immunologically virgin subjects. If so, then other (undefined) factors besides the level of preexisting immunity must play a role in the epidemiology of influenza.

Avian and Swine Influenza Viruses Aquatic birds are the largest reservoir of influenza A viruses, harboring 16 hemagglutinin (H1–H16) and nine neuraminidase (N1–N9) subtypes. (In addition, H17N10 and H18N11 viruses are found in bats.) Influenza A pandemic strains in 1957 (A/H2N2) and in 1968 (A/H3N2) resulted from reassortment of gene segments between human and avian viruses. The influenza A/H1N1 virus that caused the most severe pandemic of modern times (1918–1919) appears to have been an adaptation of an avian virus to human infection. Thus, there is concern that avian influenza viruses with novel hemagglutinin and neuraminidase antigens have the potential to emerge as pandemic strains.

Avian influenza A viruses have been reported to cause sporadic cases and small outbreaks in humans, usually after direct contact with birds (most commonly poultry). Sustained person-to-person transmission in the community has not been observed. Avian influenza A/H5N1 virus has been noted to cause illness in humans since 1997, with 648 cases reported to the World Health Organization as of January 2014. It is not clear whether the high observed case–fatality rate (59%) reflects preferential detection of severe cases. A/H7N7 infections have been noted in poultry industry workers; conjunctivitis was the most prominent feature, although a minority of individuals also had respiratory illness. More than 333 cases of avian A/H7N9 infection have been reported in China, with case–fatality rates of 36% among the infected patients admitted to the hospital. Most H7N9 isolates are sensitive to neuraminidase inhibitors, but a few isolates have exhibited high-level resistance to oseltamivir and diminished sensitivity to zanamivir. Infections with avian H9N2 viruses have been reported primarily among children in Hong Kong and have consisted largely of mild respiratory illnesses. Mild cases of illness due to influenza H10N7 virus in Egypt and Australia have also been reported. In 2013, the first cases of human infection with avian A/H10N8 and H6N1 viruses were described.

Influenza A viruses also circulate in swine but rarely infect humans. Whereas humans primarily have α-2,6-galactose receptors for hemagglutinins and birds primarily have α-2,3-galactose receptors, swine have both types of receptors. Thus, swine hosts efficiently sustain simultaneous infection with both human and avian viruses, thereby facilitating reassortment of genetic segments between viruses of both species. The pandemic A/H1N1 strain of 2009–2010 was a quadruple reassortant among swine, avian, and human influenza viruses. The influenza A virus subtypes that circulate most commonly in swine are H1N1, H1N2, and H3N2. When a predominantly swine virus causes infections in humans, it is designated a variant virus by the addition of "v" after the subtype. For example, influenza A/H3N2v virus was responsible for 321 cases of human infection reported in the United States in 2011 and 2012 and for 18 cases in 2013. Almost all of the affected patients had had close contact with swine. Only limited person-to-person transmission of swine influenza virus has been