noted. Since 2005, 16 human cases caused by A/H1N1v virus and 5 caused by A/H1N2v virus have been detected in the United States.

**Influenza B and C Viruses** Influenza B virus causes outbreaks that are generally less extensive and are associated with less severe disease than those caused by influenza A virus, although the disease may occasionally be severe. The hemagglutinin and neuraminidase of influenza B viruses undergo less frequent and less extensive variation than those of influenza A viruses; this characteristic may account, in part, for the lesser severity of influenza B. Outbreaks of influenza B occur most frequently in schools and military camps, although outbreaks in institutions in which elderly individuals reside have also been noted on occasion. Since the 1980s, two antigenically distinct "lineages" of influenza B virus have circulated: Victoria and Yamagata.

In contrast to influenza A and B viruses, influenza C virus appears to be a relatively minor cause of disease in humans. It has been associated with common cold–like symptoms and occasionally with lower respiratory tract illness. The widespread prevalence of serum antibody to this virus indicates that asymptomatic infection may be common.

**Influenza-Associated Morbidity and Mortality Rates** Rates of morbidity and mortality caused by influenza outbreaks continue to be substantial. Most individuals who die in this setting have underlying diseases that place them at high risk for complications of influenza (Table 224-2). On average, there were 226,000 influenza-associated hospitalizations per year in the United States in 1979–2001. Recently, the moderately severe influenza season in 2012–2013 was associated with 381,500 hospitalizations (42 per 100,000 persons). Excess annual hospitalizations for groups of adults and children with high-risk medical conditions ranged from 40 to 1900 per 100,000 during outbreaks of influenza in 1973–2004. The most prominent high-risk conditions are chronic cardiac and pulmonary diseases and old age. Mortality rates among individuals with chronic metabolic or renal diseases or certain immunosuppressive diseases have also been elevated, although they remain lower than mortality rates among patients with chronic cardiopulmonary diseases. In the pandemic of 2009–2010, increased risk of severe disease was noted in children from birth to 4 years of age and in pregnant women. The morbidity rate attributable to influenza in the general population is considerable. It is estimated that interpandemic outbreaks of influenza currently incur annual economic costs of more than $87 billion in the United States. For pandemics, it is estimated that annual economic costs would range from $89.7 to $209.4 billion for attack rates of 15–35%.

## PATHOGENESIS AND IMMUNITY

The initial event in influenza is infection of the respiratory epithelium with influenza virus acquired from respiratory secretions of acutely infected individuals. In all likelihood, the virus is transmitted via aerosols generated by coughs and sneezes, although transmission through hand-to-hand contact, other personal contact, and even fomites may take place. Experimental evidence suggests that infection by a small-particle aerosol (particle diameter <10 μm) is more efficient than that by larger droplets. Initially, viral infection involves the ciliated columnar epithelial cells, but it may also involve other respiratory tract cells, including alveolar cells, mucous gland cells, and macrophages. In infected cells, virus replicates within 4–6 h, after which infectious virus is released to infect adjacent or nearby cells. In this way, infection spreads from a few foci to a large number of respiratory cells over several hours. In experimentally induced infection, the incubation period of illness has ranged from 18 to 72 h, depending on the size of the viral inoculum. Histopathologic study reveals degenerative changes, including granulation, vacuolization, swelling, and pyknotic nuclei in infected ciliated cells. The cells eventually become necrotic and desquamate; in some areas, previously columnar epithelium is replaced by flattened and metaplastic epithelial cells. The severity of illness is correlated with the quantity of virus shed in secretions; thus, the degree of viral replication itself may be an important factor in pathogenesis. Despite the frequent development of systemic signs and symptoms such as fever, headache, and myalgias, influenza virus has only rarely been detected in extrapulmonary sites (including the bloodstream). Evidence suggests that the pathogenesis of systemic symptoms in influenza may be related to the induction of certain cytokines, particularly tumor necrosis factor α, interferon α, interleukin 6, and interleukin 8, in respiratory secretions and in the bloodstream.

The host response to influenza infections involves a complex interplay of humoral antibody, local antibody, cell-mediated immunity, interferon, and other host defenses. Serum antibody responses, which can be detected by the second week after primary infection, are measured by a variety of techniques: hemagglutination inhibition (HI), complement fixation (CF), neutralization, enzyme-linked immunosorbent assay (ELISA), and antineuraminidase antibody assay. Antibodies to the hemagglutinin appear to be the most important mediators of immunity; in several studies, HI titers of ≥40 have been associated with protection from infection. Secretory antibodies produced in the respiratory tract are predominantly of the IgA class, and secretory antibody neutralization titers of ≥4 have also been associated with protection. A variety of cell-mediated immune responses, both antigen-specific and antigen-nonspecific, can be detected early after infection and depend on the prior immune status of the host. These responses include T cell proliferative, T cell cytotoxic, and natural killer cell activity. In humans, CD8+ as well as CD4+ T lymphocytes are directed at conserved regions of internal proteins (NP, M, and P) as well as at the surface proteins H and N. Interferons can be detected in respiratory secretions shortly after the shedding of virus has begun, and rises in interferon titers coincide with decreases in virus shedding.

The host defense factors responsible for cessation of virus shedding and resolution of illness have not been defined specifically. Virus shedding generally stops within 2–5 days after symptoms first appear, at a time when serum and local antibody responses often are not detectable by conventional techniques, although antibody rises may be detected earlier by use of highly sensitive techniques, particularly in individuals with previous immunity to the virus. It has been suggested that interferon, cell-mediated immune responses, and/or nonspecific inflammatory responses all contribute to the resolution of illness. CD8+ cytotoxic T lymphocyte responses may be particularly important in this regard.

**TABLE 224-2 PERSONS AT HIGHER RISK FOR COMPLICATIONS OF INFLUENZA OR FOR INFLUENZA-RELATED VISITS TO HEALTH CARE FACILITIES**

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| All children from birth to <5 years, especially <2 years |
| All persons ≥50 years old |
| Pregnant women |
| Adults and children who have chronic pulmonary (including asthma) or cardiovascular (except isolated hypertension), renal, hepatic, neurologic, hematologic, or metabolic disorders (including diabetes mellitus) |
| Persons who have immunosuppression (including that caused by medications or by HIV infection) |
| Children and adolescents (6 months to 18 years old) who are receiving long-term aspirin therapy and who might be at risk for Reye's syndrome after influenza virus infection |
| Residents of nursing homes and other long-term care facilities |
| Native Americans/Alaska Natives |
| Persons who are morbidly obese (body mass index ≥40 kg/m$^2$) |

## CLINICAL MANIFESTATIONS

Influenza is most frequently described as a respiratory illness characterized by systemic symptoms, such as headache, feverishness, chills, myalgia, and malaise, as well as accompanying respiratory tract signs and symptoms, particularly cough and sore throat. In some cases, the onset is so abrupt that patients can recall the precise time they became ill. However, the spectrum of clinical presentations is wide, ranging from a mild, afebrile respiratory illness similar to the common cold (with either a gradual or an abrupt onset) to severe prostration with relatively few respiratory signs and symptoms. In most of the cases that come to a physician's attention, the patient has a fever, with temperatures of 38°–41°C (100.4°–105.8°F). A rapid temperature rise within the first 24 h of illness is generally followed by gradual defervescence over 2–3 days, although, on occasion, fever may last as long as 1 week.