

# 96 - 206 Influenza

## 206 Influenza

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**Influenza ■ ■ DEFINITION** The term influenza represents both a clinically defined respiratory illness accompanied by systemic symptoms of fever, malaise, and myalgia and the name of the orthomyxoviruses that cause this syndrome. Although this term is sometimes used more generally to denote any viral respiratory illness, many features distinguish influenza from these other illnesses, most particularly its systemic symptoms, its propensity to cause sharply peaked winter epidemics in temperate climates, and its capacity to spread rapidly among close contacts. The morbidity and mortality associated with influenza epidemics are documented closely in the United States by the Centers for Disease Control and Prevention (CDC), which records clinical cases of influenza-like illness, cases of virologically documented influenza, and excess deaths due to pneumonia and influenza combined. ■ ■ **ETIOLOGIC AGENTS** Three influenza viruses occur in humans: A, B, and C. These viruses are irregularly circular in shape, measure 80–120 nm in diameter, and have a lipid envelope and prominent spikes that are formed by the two surface glycoproteins, hemagglutinin (H) and neuraminidase (N) (Fig. 206-1). The hemagglutinin functions as the viral attachment protein, binding to sialic acid receptors on the cells that line the superficial epithelium of the respiratory tract. The neuraminidase cleaves the virus from the cell membrane to facilitate its release from the cell and prevents self-aggregation of viruses. Influenza A viruses have eight single-strand negative-sense RNA segments in their genomes that encode hemagglutinin and neuraminidase as well as internal genes, including polymerase, matrix, nucleoprotein, and nonstructural genes. The segmented nature of the genome allows gene reassortment; an analogy for reassortment is the shuffling of a deck of cards. Reassortment takes place when a single cell is infected with two different strains of influenza. **PART 5 Infectious Diseases** Among the influenza viruses, the A viruses are of paramount importance for several reasons: (1) the plasticity of their genomes, which enables them to react to the prevailing immunity in the community by modifying their immunogenic epitopes, particularly on the hemagglutinin surface protein (antigenic drift); (2) the segmentation of their genomes, which allows genes coding both surface and internal proteins to be reassorted between influenza A variants (antigenic shift); and (3) their extensive mammalian and avian reservoirs, in which multiple variants with distinct hemagglutinin and neuraminidase genes lie in wait. As a result of all of these factors, influenza A virus has the ability, particularly after an antigenic shift, to cause a worldwide epidemic (pandemic). The most severe influenza A pandemic in modern history **FIGURE 206-1** An electron micrograph of influenza A virus (×40,000). (From YZ Cohen, R Dolin: Influenza, in Harrison's Principles of Internal Medicine, 19th ed. DL Kasper et al [eds]. New York: McGraw-Hill, 2015, p 1209.)

took place in 1918; ~50 million deaths were attributed to the culpable influenza A H1N1 virus in the years surrounding 1918. The influenza A viruses are further classified by their surface glycoproteins (H and N), the geographic location of their isolation, their sequential number among isolated viruses, and their year of isolation. Thus, for the 2024–2025 season, U.S.-licensed egg-based influenza vaccines will contain hemagglutinin derived from an influenza A/Victoria/4897/2022 (H1N1) pdm09-like virus, an influenza A/Thailand/8/2022 (H3N2)-like virus, and an influenza B/Austria/

1359417/2021 (B/Victoria lineage)-like virus. U.S. cell culture-based inactivated and recombinant influenza vaccines will contain HA derived from an influenza A/Wisconsin/67/2022 (H1N1) pdm09-like virus, an influenza A/Massachusetts/18/2022 (H3N2)-like virus, and an influenza B/Austria/1359417/2021 (B/Victoria lineage)-like virus. ■ ■ **EPIDEMIOLOGY** Influenza virus causes outbreaks during the cooler months of the year and thus has a mirror-image season in the antipodes compared with that in the Northern Hemisphere. The circulation of strains in the Southern Hemisphere has some predictive value for vaccine composition in the Northern Hemisphere, and vice versa. This information is important as the degree of antigenic drift is one determinant of vaccine efficacy. Vaccine composition typically must change in at least one component yearly in anticipation of the predicted circulating strains. A typical outbreak begins in early winter and lasts 4–5 weeks in a given community, although its impact on the country as a whole will be of considerably longer duration. When influenza activity exceeds a predetermined baseline, an influenza outbreak is classified as an epidemic. Influenza's impact is reflected in increased school and work absenteeism, increased visits to emergency departments and primary care physicians, and increased hospitalizations, particularly of older persons and individuals with underlying cardiopulmonary disease. The impact often is most easily recognized in the pediatric population, whose school absenteeism quickly peaks. Influenza's global spread and causative strain(s) in a given year are well documented by the surveillance networks of the World Health Organization (WHO) and the CDC. The severity of an epidemic depends on the transmissibility and virulence of the viral strain, the susceptibility of the population, the adaptation of the virus to its human host, and the degree of antigenic match to the recommended vaccine. None of these parameters is totally predictable for influenza A. Influenza is largely spread by small- and large-particle droplets; however, emerging data support a role for aerosol transmission. Transmission is likely modulated by temperature and humidity. Spread is facilitated by the coughing and sneezing that accompany the illness. Within families, the illness is often introduced by a preschool or school-aged child. In the United States, influenza virus circulation in the first quarter of 2020 declined sharply within 2 weeks of the COVID-19 emergency declaration and widespread implementation of community mitigation measures and travel restrictions. The decline occurred in other Northern Hemisphere countries and the tropics, and in 2020, Southern Hemisphere temperate climates had virtually no influenza circulation. Influenza activity remained at low levels during the 2020–2021 Northern Hemisphere season, and increased in seasons thereafter. While changes in health care-seeking behavior and testing priorities during the pandemic may have contributed, such declines in influenza detection were noted even in areas with continued or increased testing, implicating community mitigation measures as the most likely reason. Influenza A Viruses When a major shift in the hemagglutinin and/or the neuraminidase occurs, with introduction of a new serotype from an animal or avian reservoir, an influenza A strain has the potential to cause a pandemic. In modern influenza history, such shifts occurred in 1918 (H1N1), 1957 (H2N2), 1968 (H3N2), 1977 (H1N1), and 2009 (H1N1pdm) (Table 206-1). On the basis of

analysis of serum antibody profiles in the elderly, epidemics that took place in the 1890s have been attributed to H3N2 and H2N2 viruses. Epidemics typical of influenza have been documented throughout recorded history.

TABLE 206-1 Emergence of Antigenic Subtypes of Influenza A Virus Associated with Pandemic or Epidemic Disease

| YEARS     | SUBTYPE                | EXTENT OF OUTBREAK |
|-----------|------------------------|--------------------|
| 1889–1890 | H2N8a                  | Severe pandemic    |
| 1900–1903 | H3N8a                  | Moderate epidemic  |
| 1918–1919 | H1N1b (formerly HswN1) | Severe pandemic    |
| 1933–1935 | H1N1b (formerly H0N1)  | Mild epidemic      |
| 1946–1947 | H1N1                   | Mild epidemic      |
| 1957–1958 | H2N2                   | Severe pandemic    |
| 1968–1969 | H3N2                   | Moderate pandemic  |
| 1977–1978 | c H1N1                 | Mild pandemic      |
| 2009–2010 | d H1N1                 | Pandemic           |

aAs determined by retrospective serologic survey of individuals alive during those years (“seroarchaeology”). bHemagglutinins formerly designated as Hsw and H0 are now classified as variants of H1. cFrom this time until 2016–2017, viruses of the H1N1 and H3N2 subtypes circulated in alternating years or concurrently. dA novel influenza A/H1N1 virus emerged to cause this pandemic. Source: Adapted from YZ Cohen, R Dolin. Influenza. In: Kasper DL, et al, eds. Harrison’s Principles of Internal Medicine, 19th ed. New York, McGraw-Hill, 2015,

p. 1209. In some epidemics, a younger age group proves especially susceptible. This is the case with current H1N1 epidemics, where individuals born before 1968 had likely been exposed to related viral strains and thus were relatively protected against the current strain. The 1918 epidemic was striking in this regard: the most severely infected individuals were infants and previously healthy young adults—the latter being a group not typically found to have high influenza mortality (Fig. 206-2). The 1918 epidemic increased all-cause mortality and led to more deaths than all military losses in World War I. Despite the attention paid to the risk and impact of pandemic disease, it is generally appreciated that—with the exception of 1918—cumulatively more illness occurs during yearly epidemics combined than in pandemics. All of

Pneumonia/influenza mortality rate per 100,000 <1 Year

65–74 Years

25–34 Years

Influenza epidemics with excess pneumonia/influenza mortality >20/100,000

FIGURE 206-2 Excess pneumonia/influenza deaths in 1900–1953, demonstrating the dramatic peaks of deaths among young infants and young adults (25–34 years of age) in 1918. (Data are from public health records collated by PF Wright.)

the annual influenza A epidemics in the past 50 years have been caused by H1N1 and/or H3N2 strains. H2N2 strains circulated between 1957 and 1968, and H1N1 strains circulated prior to that, including in 1918.

Avian Influenza Viruses Wild birds are considered the natural hosts for influenza viruses, and potential pandemic viruses continue to emerge with higher-numbered hemagglutinins (e.g., H5, H6, H7, H8, H9) reflecting some of the 18 distinct H subtypes in avian reservoirs. Bird migration contributes to rapid global spread. Highly pathogenic influenza H5 and H7, in particular, have been associated with wide spread outbreaks in poultry, human infections through contact with infected birds, and limited human-to-human transmission. Most human infections have occurred in

individuals who have had direct contact with domesticated birds or who have visited live-bird markets. Some avian strains—notably H5 strains—are highly pathogenic in humans, as was the 1918 strain. The reasons for the high pathogenicity of certain strains are not entirely clear. After the sequencing of the 1918 virus recovered from the lungs of bodies buried in the Arctic permafrost, the virus was genetically reconstructed under carefully controlled isolation conditions. In animal studies of this viable 1918 virus, both the hemagglutinin and the ribonucleoprotein contributed to high levels of replication accompanied by an abnormally enhanced innate immune response characterized by proinflammatory cytokines. Perhaps this “cytokine storm” is the best explanation for the enhanced illness in young, immunologically vigorous individuals during the 1918 pandemic. Sequencing demonstrated that the 1918 virus was of avian origin. Although the 1918 virus was first identified in military camps in the United States, its impact cannot be attributed to the disruption of war—the illness was well documented in countries such as Iceland that were not directly involved in World War I.

CHAPTER 206 The same concerns about a “cytokine storm” have been raised about the H5N1 viruses that first emerged in Hong Kong in 1996. These viruses exhibited high pathogenicity in individuals who had direct contact with domestic fowl, with mortality rates close to 50%, but also displayed poor human-to-human transmissibility. Pathogenicity appears to be a function not just of the viruses’ surface proteins, but also of an optimal gene constellation including all eight segmented influenza genes. However, unlike the 1918 strain, the H5N1 viruses have, to date, caused only sporadic disease, as have other limited clusters of a highly pathogenic H7N9 virus. Influenza Sporadic H5 avian infections have been reported in many mammals, including sea lions, sea elephants, foxes, goats, and zoo animals. In 2024, a multistate outbreak of highly pathogenic H5 avian influenza in dairy cows was first reported, with rare human infections from animal exposures. It is unclear why higher-numbered avian hemagglutinin strains have not acquired the degree of transmissibility necessary to cause pandemic disease.

Swine Influenza Viruses Swine play an important role in interspecies transmission of influenza. It is postulated that epithelial cells in the swine respiratory tract may play a specific role as a “mixing vessel,” allowing the reassortment of genes from avian and human sources and thereby permitting the transmission of avian viruses to humans. The nature of the sialic acid receptors for influenza virus hemagglutinin partially accounts for host preference. Humans have largely  $\alpha$ -2,6galactose receptors, while birds have  $\alpha$ -2,3-galactose receptors. Swine have both types of receptors on their respiratory epithelial cells—hence their postulated role in facilitating reassortment and host adaptation of avian strains to growth in humans. The swine origin 2009 H1N1pdm strain was a reassorted virus with gene segment origins from avian, human, and swine hosts.

Influenza B and C Viruses The influenza B viruses are more genetically stable than the influenza A viruses and are mainly associated with human infection. Two lineages of influenza B have circulated for the past 40 years (B/Yamagata-like and B/Victoria-like viruses), and it has proven difficult to predict which strain will be dominant in a given year. Co-circulation of both B lineages—Victoria and Yamagata—began in 2011. This led to the incorporation of representatives of both influenza A lineages plus influenza A/H1N1 and H3N2

Deaths 4,900–51,000 Hospitalizations 100,000–710,000 Illnesses 9,300,000–41,000,000

FIGURE 206-3 Pyramid of impact of influenza illness. Estimated range of annual burden of influenza in the United States from 2010–2023. (From [https://www.cdc.gov/flu-burden/php/about/index.html?CDC\\_AAref\\_Val=https://www.cdc.gov/flu/about/burden/index.](https://www.cdc.gov/flu-burden/php/about/index.html?CDC_AAref_Val=https://www.cdc.gov/flu/about/burden/index.))

viruses into quadrivalent vaccines, first marketed in the United States in 2013. However, since March 2020, B/Yamagata influenza viruses have not circulated in the population. Thus, influenza

vaccines in the United States will revert to a trivalent vaccine for the 2024–2025 season, containing only a B/Victoria-like virus. Influenza C viruses cause intermittent mild disease. The clinical information about this virus is limited because of the small number of isolated viruses compared to influenza A or B viruses. Influenza-Associated Morbidity and Mortality Influenza virus infects people of all ages and causes mild to severe illness, and even death in some cases. The impact of influenza is highly variable from year to year and can be depicted as a pyramid of illnesses, medical visits, hospitalizations, and deaths (Fig. 206-3). Infection rates are highest among children, with complications and hospitalizations from seasonal influenza being greatest among certain high-risk groups during most epidemics. These groups are assigned the highest priority for vaccination and other preventive and therapeutic measures. Their caregivers and close contacts are also prioritized targets of interventions (Table 206-2). PART 5 Infectious Diseases Mortality attributable to influenza, reported as excess over the anticipated sine-wave curve of pneumonia and influenza deaths during the year, varied between 4900 and 51,000 deaths annually from 2010 to 2023. The dramatic effect of the COVID-19 pandemic on excess pneumonia and influenza mortality data is evident from the comparison of 2020 data with data from the prior three seasons (Fig. 206-4). Due to this outsized effect of COVID-19, the method for calculating mortality due to influenza changed starting with the 2023–2024 season and is now restricted to percentage of deaths with influenza listed on the death certificate. In contrast to mortality surveillance in adults, influenza-associated pediatric mortality is based on laboratory confirmation. Upon normalization of influenza circulation after the COVID-19 pandemic, 184 children died in 2022–2023 and 138 children died in 2023–2024 from laboratory-confirmed influenza. These numbers are undoubtedly underestimates, since all children are not tested for influenza, and even among those who are tested, tests are less sensitive later in the illness. ■ ■ PATHOGENESIS AND IMMUNITY At a cellular level, influenza virus binds to sialic acid receptors and enters the epithelial cell through receptor-mediated endocytosis. The virus then enters an endosome, where acidification promotes proteolytic cleavage of the hemagglutinin, exposing a fusion domain. The influenza hemagglutinin undergoes a marked structural reorganization in this cleavage step. Hemagglutinin cleavage may be one of the factors that restrict viral growth to epithelial cells, as a unique protease in the respiratory milieu is required for this cleavage to occur. The fusion domain allows the viral RNA to enter the cytoplasm. The nucleoprotein is transported into the nucleus of the cell, where transcription to a positive-sense RNA and replication take place. Viral proteins then assemble on the apical surface of the infected cell and, after incorporation of cellular membrane, bud from the membrane back into the mucosal milieu.

TABLE 206-2 High-Risk Groups Who Should Be Assigned a High Priority for Influenza Immunization and Treatment

|                                                                                                                                                                                                 |                                                                                       |                                                                                                                                                                                                                                                                                  |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| High-Risk Group                                                                                                                                                                                 | Children 6–59 months of age                                                           | Adults $\geq 50$ years of age                                                                                                                                                                                                                                                    |
| Persons with chronic pulmonary (including asthma), cardiovascular (except isolated hypertension), renal, hepatic, neurologic, hematologic, or metabolic disorders (including diabetes mellitus) | Persons who are immunocompromised (any cause, including medications or HIV infection) | Women who are or plan to be pregnant during the influenza season                                                                                                                                                                                                                 |
| Children and adolescents (6 months through 18 years of age) who are receiving aspirin- or salicylate-containing medications and who might be at risk for Reye syndrome                          | Residents of nursing homes and other long-term-care facilities                        | American Indians/Alaska Natives                                                                                                                                                                                                                                                  |
| Persons who are extremely obese (body mass index $\geq 40$ )                                                                                                                                    | Contacts and Caregivers                                                               | Caregivers and contacts of those at risk: health care personnel in inpatient and outpatient care settings who have the potential for exposure to patients or to infectious materials, medical emergency-response workers, autopsy personnel, employees of nursing home and long- |

term-care facilities who have contact with patients or residents, and students and trainees in these professions who have contact with patients Household contacts and caregivers of children  $\leq 59$  months (i.e.,  $< 5$  years) of age (particularly contacts of infants  $< 6$  months old) and adults  $\geq 50$  years of age Household contacts (including children) and caregivers of persons who are in a high-risk group aNo hierarchy is implied by order of listing. Source: Centers for Disease Control and Prevention 2023–2024 summary of recommendations for influenza vaccine (<https://www.cdc.gov/mmwr/volumes/72/rr/rr7202a1.htm>). Influenza infection is initiated in the upper respiratory tract via aerosolized virus. The cells infected with influenza virus are primarily the ciliated cells of the respiratory tract. Denudation of the superficial epithelium probably accounts for much of the symptomatology and may predispose to secondary bacterial infections. The onset of symptoms follows an incubation period that, for a viral illness, is very short: 48–72 h. The infection spreads to the lungs but, even there, remains confined to the epithelial layer. Influenza virus is associated with systemic symptoms of fever, malaise, and myalgia. These manifestations are presumed to be mediated by cytokines, and excess cytokine production has been implicated in the acute toxicity of H5N1 and other highly pathogenic influenza viruses. The immune response to influenza virus occurs at the systemic and mucosal levels and involves both T and B cells. The B-cell responses are directed primarily toward antigenic epitopes on the two surface glycoproteins—i.e., hemagglutinin and neuraminidase. At a structural level, the four recognized epitopes on the hemagglutinin are largely confined to the globular head of the protein, which collectively constitute the targets for hemagglutination inhibition (HAI) antibodies. HAI and neutralizing antibodies are highly correlated; HAI antibody levels are used as a measure of susceptibility to clinical infection and thus as a measure of vaccine-induced protection. In a child or an adult without prior vaccination or with the emergence of a distinctly new strain, serum HAI antibody is a surrogate for protection. However, in individuals with both vaccine-induced and natural immunity, the protective efficacy of a vaccine based on serum HAI antibody is more difficult to predict. There is considerable research interest in the induction and protective role of broadly neutralizing antibodies that recognize less antigenically variable regions on the stalk of the hemagglutinin. The results of these studies have led to investments toward research and development of a universal influenza vaccine, although no such vaccines are yet available in clinical practice. The role of T-cell immunity, which primarily recognizes internal protein epitopes, remains unclear in humans. However, T-cell

Pneumonia, Influenza, and COVID-19 Mortality from the National Center for Health Statistics Mortality Surveillance System

Number of influenza coded deaths Number of COVID-19 coded deaths % of deaths due to PIC  
Baseline Threshold

% of all deaths due to PIC

Epidemic threshold

Seasonal baseline

MMWR week

FIGURE 206-4 Pneumonia, influenza, and COVID-19 mortality. MMWR, Morbidity and Mortality Weekly Report; PIC, pneumonia, influenza, COVID-19. Data through the week ending January 23, 2021, as of January 28, 2021. (From [https://www.cdc.gov/fluview/?CDC\\_AAref\\_Val=https://www.cdc.gov/flu/weekly/index](https://www.cdc.gov/fluview/?CDC_AAref_Val=https://www.cdc.gov/flu/weekly/index))

immunity is thought to play a role in clearance of an influenza infection that quite reproducibly develops 8–10 days after exposure. A role for T cells in protection against acquisition of infection has also been proposed. CLINICAL MANIFESTATIONS Attack rates of clinical influenza vary considerably from year to year. With the advent of molecular diagnostic tests, prospective studies with regular sampling demonstrate that asymptomatic or minimally symptomatic cases of influenza are more common than previously recognized. When symptomatic, influenza is primarily a respiratory illness causing cough, sore throat, and rhinorrhea or nasal congestion. The illness has a sudden onset and is epidemiologically linked to close contact with persons who have similar symptoms and often to community-wide respiratory illness. What distinguishes influenza from most other respiratory viral illnesses is the degree of accompanying fever, chills, fatigue, myalgia, and malaise. SARS-CoV-2 is the exceptional respiratory virus that also has a remarkable systemic component (Chaps. 204 and 205). Symptoms of influenza typically begin within 48–72 h of exposure. Respiratory symptoms, particularly recurrent cough, persist well beyond the 2–5 days of systemic symptoms. There is a postinfectious delay in return to normal levels of activity. Pulmonary function is persistently decreased after acute influenza. Persons with a regular exercise routine (e.g., runners) note a decrease from their prior level of performance that typically lasts for a month or more. In the elderly, the respiratory presentation may be less prominent, but there is often a decline in baseline activity and a loss of appetite. On physical examination, the patient with influenza appears ill, with sweating, coughing, nonpurulent conjunctivitis, and diffuse pharyngeal erythema. With lower respiratory involvement, pulmonary examination typically reveals nonlocalizing scattered rales, rhonchi, and wheezes. When present, localized pulmonary findings suggest relatively complicated pneumonia with a bacterial component. Muscle

#### Number of deaths

CHAPTER 206 Influenza pain may be elicited by pressure, particularly in the calves and thighs. There are rare gastrointestinal findings. No rash is associated with influenza. ■ ■

#### COMPLICATIONS

Most persons who become ill with influenza virus infection recover without serious complications or sequelae. Complications of influenza occur most commonly in persons  $\geq 65$  years of age, young children, persons of all ages with underlying cardiopulmonary disease and immunosuppression, and women who are in the second or third trimester of pregnancy. Respiratory Complications Pneumonia characterized by progressive air hunger, localized pulmonary findings on physical examination, and radiographic findings of diffuse infiltrates or consolidation is the most common complication of influenza. Pneumonia in influenza can be primary influenza viral pneumonia, secondary bacterial pneumonia, or mixed viral and bacterial pneumonia. Primary viral pneumonia is characterized by increasing dyspnea, persistent fever, and—in more severe cases—cyanosis. Primary influenza pneumonia was typical in the 1918 pandemic and occurs with H5N1 virus, as initially described in Hong Kong in 1997. Pathologically, a marked inflammatory reaction in the alveolar septa is characterized by infiltration of monocytes, lymphocytes, and macrophages, with variable numbers of neutrophils. Destruction and hemorrhage are seen in the respiratory epithelium. Large amounts of virus can be recovered from the lungs. In secondary bacterial pneumonia or mixed viral and bacterial pneumonia, illness may be biphasic, with evidence of

recovery from the primary influenza illness followed by recrudescence of fever and pulmonary symptoms. Localizing findings may be detected on pulmonary examination and/or x-ray. The development of secondary bacterial infection is not surprising, as influenza de-epithelializes the airways and destroys ciliary function, allowing bacterial contamination. Another proposed mechanism for bacterial/viral enhancement is

the production by *Staphylococcus* and *Pseudomonas* of proteases that enhance cleavage of the influenza hemagglutinin and thereby facilitate viral replication. The risk of secondary bacterial disease is greatest in elderly patients and those with chronic obstructive pulmonary disease (COPD).

Some influenza strains cause laryngotracheobronchitis, bronchiolitis, or croup in children. Otitis media—a common accompaniment to influenza in children—may also be due to a combination of influenza virus and bacteria. Extrapulmonary Complications Although influenza is believed to spread only rarely beyond the respiratory epithelial cells, where unique endogenous proteases facilitate hemagglutinin cleavage and productive infection, this disease causes not only prominent systemic complaints but also a variety of extrapulmonary manifestations. The most common extrapulmonary manifestation of influenza is myositis, which is seen more often in influenza B and is characterized by severe muscle pain, elevated creatine phosphokinase levels, and myoglobinuria that can lead to renal failure. The muscles are extremely tender to touch. Myo-/pericarditis is seen less frequently. However, a consistent epidemiologic link exists between influenza epidemics and excess cardiovascular hospitalizations. Neurologic involvement, while rare, does occur following influenza infection. Influenza-associated encephalopathy or encephalitis is characterized by rapid progression within a few days of influenza infection. Transverse myelitis and parkinsonian symptoms have been reported. Postinfectious acute demyelinating encephalomyelitis can follow influenza as well as other viral infections. Neurologic manifestations are more frequent in children as compared to adults. Children most commonly present with febrile seizures, increased seizure frequency among those with seizure disorders, or self-limited encephalopathy. More serious manifestations of meningitis, encephalitis, and focal brain lesions may occur, particularly in children with preexisting neurologic conditions. PART 5 Infectious Diseases Guillain-Barré syndrome can develop after influenza and was reported after a widespread influenza vaccination effort in the fall of 1976 that was undertaken in anticipation of a swine influenza epidemic (which never materialized). Until aspirin was recognized as a cofactor in its precipitation, Reye syndrome, an acute hepatic decompensation, was seen commonly in children and adolescents with influenza, particularly those infected with influenza B virus. Subsequently, the use of aspirin for fever control and symptom relief in children with viral infections was strongly discouraged, and Reye syndrome has virtually disappeared from clinical practice. ■ ■LABORATORY FINDINGS AND DIAGNOSIS There is a strong argument for establishing a microbiologic diagnosis from both an individual-patient and a public-health perspective. This information is particularly valuable early in the season, when the extent of influenza and the precise circulating strain(s) are uncertain; in the management of high-risk or hospitalized patients; in settings such as long-term-care facilities and hospitals, where the institution of specific infection-control measures is appropriate; and in any patient with influenza-like illness if the test results will influence clinical management. Influenza virus is most easily recovered from nasal or pharyngeal specimens. A number of rapid influenza diagnostic tests (RIDTs) are TABLE 206-3 Categories of Vaccines Licensed for Prevention of Seasonal Influenza, United States LIVE ATTENUATED STANDARD INACTIVATED HIGH-DOSE INACTIVATED

RECOMBINANT ADJUVANTED INACTIVATED Route Intranasal Intramuscular Intramuscular  
 Intramuscular Intramuscular Approved ages 2–49 years ≥6 months ≥65 years ≥18 years ≥65  
 years HAa

Substrate Eggs Eggs/cell culture Eggs Cell culture Eggs Number of strains

aHemagglutinin content in micrograms per strain.

available. They work by detecting viral antigens and can provide results within 10–15 min. Rapid molecular assays (i.e., nucleic acid amplification tests [NAATs]) detect viral genetic material. Several NAATs are authorized for home use, including tests that detect and differentiate between SARS-CoV-2, influenza A, and influenza B in self-collected anterior nasal swab samples. In addition to RIDTs and rapid molecular assays, several influenza diagnostic tests are available in specialized hospital and public health laboratories, including reverse transcription polymerase chain reaction (RT-PCR) and viral culture. Many nucleic acid-based tests are multiplex and target a panel of common respiratory pathogens— influenza, respiratory syncytial virus, parainfluenza virus, and coronaviruses including SARS-CoV-2—an advantage in the ill hospitalized patient and during outbreaks of other respiratory pathogens. Clinicians should not use viral culture for initial or primary diagnosis of influenza because results will not be available in a timely manner to inform clinical management, but viral culture can confirm the strain and allow for antiviral sensitivity testing. Serologic confirmation of infection is also possible but requires paired serum samples, with the convalescent-phase sample obtained 2 weeks after infection. Other laboratory tests are of limited value. Mild leukopenia is seen in influenza, and a white blood cell count  $>15,000/\mu\text{L}$  suggests a secondary bacterial component in influenza pneumonia. ■ ■

**DIFFERENTIAL DIAGNOSIS** Influenza may be diagnosed clinically based on an acute presentation of a febrile respiratory illness during high periods of influenza circulation. However, less common presentations of influenza and cases occurring outside of peak influenza season are frequently misdiagnosed on the basis of symptoms alone. Influenza symptoms and signs may overlap with symptoms of other respiratory viruses. Respiratory syncytial virus often co-circulates with influenza virus; it particularly affects the youngest children, causing bronchiolitis, but it can also infect the elderly, leading to an influenza-like nonspecific respiratory illness and a decline in mobility, nutrition, and pulmonary function, with resultant hospitalization. Persons with COVID-19 have a wide range of symptoms reported, ranging from mild to severe illness. Many of these symptoms—fever, chills, cough, shortness of breath, fatigue, muscle aches, headaches, congestion or runny nose—overlap with the symptoms of influenza. While new loss of taste (ageusia) or smell (anosmia) may distinguish COVID-19 from influenza, they are reported in the minority of infected persons. When SARS-CoV-2 and influenza viruses are cocirculating, clinicians should consider both viruses, as well as co-infection, in patients with acute respiratory illness symptoms. The similar clinical presentations reiterate the importance of testing in order to inform treatment decisions. ■ ■

**IMMUNIZATION** Vaccination is the best approach to prevent influenza. The vaccines currently available in the United States are increasing in number and diversity (Table 206-3). These vaccines fall into two broad categories: parenterally administered inactivated influenza vaccines and intranasally administered live-attenuated influenza vaccines. Current vaccines are further classified based on production substrate (eggs, cell), antigen dose and valence (trivalent or quadrivalent), and the presence or absence of adjuvants. Current inactivated influenza vaccines are designed with the common goal to induce immunity to the

**NONREPLICATING VACCINES**

hemagglutinin surface glycoprotein of the influenza virus. No effort is made to standardize the neuraminidase content. As the viral surface hemagglutinin undergoes frequent antigenic drift, the seasonal influenza vaccine is reformulated as often as twice annually to match the strains projected to circulate in the following influenza season. The decision about vaccine composition must be made ~10 months before the seasonal peak in influenza virus circulation; this decision is made by committees at the WHO. Subsequently, the U.S. Food and Drug Administration (FDA), which has regulatory authority over vaccines in the United States, convenes an advisory committee that considers the recommendations of WHO, reviews and discusses similar data, and makes a final decision regarding vaccine virus composition of influenza vaccines licensed and marketed in the United States. This timing can result in a mismatch of vaccine composition with the viral strains that are actually prevalent in the upcoming season. Influenza vaccine is unique in being given seasonally in the months immediately preceding an outbreak in temperate climates. In the United States, vaccine is typically available starting in August or September. The performance of current influenza vaccines varies by year, vaccine formulation, and the underlying age, health condition, and prior virus and vaccine exposure of the recipient. Unfortunately, the relative contribution of each of these factors has not been well-elucidated, given the many variables involved and the complex interplay of infection and host response. Depending on the degree to which vaccine strains match circulating strains, seasonal influenza vaccines will confer more or less protection, as antibody against influenza is for the most part strain specific. A meta-analysis of randomized controlled trials of influenza vaccine efficacy over 12 influenza seasons showed inactivated influenza vaccines had a pooled efficacy of 59% (95% confidence interval, 51–67%) among those aged 18–65 years. Since 2004–2005, the CDC has estimated the effectiveness of seasonal influenza vaccine to prevent laboratory-confirmed influenza associated with medically attended respiratory illness. During that period, effectiveness ranged from ~40 to 60% across all age groups during seasons when most circulating influenza vaccines are antigenically similar to the recommended influenza vaccine components; effectiveness was lower in years with strain mismatch. Importantly, studies support that influenza vaccine mitigates disease severity. For example, observational studies in children support that influenza vaccination reduces intensive care unit hospitalizations and deaths by an estimated 74 and 65%, respectively. Newer technologies have been developed to overcome some of the limitations of current vaccines. The first fully recombinant vaccine was approved by the FDA in 2017. Both recombinant and cell-based vaccines may overcome the egg adaptation of vaccine strains that may contribute to diminished vaccine effectiveness. Oil-in-water adjuvanted vaccines and high-dose vaccines elicit greater immune responses than traditional inactivated influenza vaccines and are approved in the United States for persons  $\geq 65$  years of age. In most head-to-head comparisons, high-dose vaccines have shown superior effectiveness to standard dose. While evidence is more limited, select comparisons of recombinant and adjuvanted vaccines with standard vaccines likewise show improved effectiveness. In head-to-head comparisons in pediatric populations in the 1990s, a live, attenuated, intranasally administered vaccine (LAIV) exhibited an efficacy exceeding that of injected inactivated vaccines. LAIV is a desirable option in children given the ease of intranasal administration and theoretical advantage of stimulating mucosal immunity by the topical route. However, in the 2014–2016 influenza seasons, LAIV had lower replicative fitness and no demonstrable efficacy assignable to the vaccine's H1N1 component. Consequently, advisory committees in the United States and elsewhere suspended the recommendations for use of LAIV until manufacturing improvements allowed reinstatement of recommendations for its use in 2018. Since that time LAIV has performed comparably to inactivated influenza vaccines in annual

effectiveness assessments. Inactivated influenza vaccines have been licensed for >60 years and have a robust safety and tolerability profile. While local reactions are most common following inactivated influenza vaccines, rare adverse

events may occur. These include Guillain-Barré syndrome, identified in 1976 and less frequently during other years; oculorespiratory syndrome, first recognized in 2000; and febrile seizures first reported in young children in Australia in 2010. Adjuvanted vaccines in general cause more local pain and erythema than unadjuvanted vaccines. LAIVs have been associated with excess wheezing and hospitalizations in children younger than 2 years and thus are not licensed for use in this age group.

The recommendations for use, the approved age range of each product, the route of administration, and the anticipated side effects are updated annually by the CDC (<https://www.cdc.gov/acip-recs/hcp/vaccine-specific/flu.html>.) In the United States, routine annual influenza vaccination is recommended for all persons 6 months of age and older. For persons 65 years of age and over, higher-dose or adjuvanted vaccines are preferred. For other age groups, no preferential recommendation is made for one influenza vaccine product over another. Two doses of vaccine should be given to children <9 years of age who have not received at least two lifetime doses of influenza vaccine prior to the start of the season. All other children should receive one dose. Groups at special risk of experiencing or transmitting influenza and for whom influenza immunization is a particularly high priority are listed in Table 206-2. History of severe allergic reaction (e.g., anaphylaxis) to any vaccine component is a contraindication to influenza vaccines. A history of Guillain-Barré syndrome within 6 weeks of a previous dose of influenza vaccine is considered a precaution for the use of all influenza vaccines. Egg allergy alone necessitates no additional safety measures for influenza vaccination beyond those recommended for any vaccine recipient, regardless of severity of previous reaction to egg.

CHAPTER 206 TREATMENT

Influenza

Influenza Antiviral therapy for influenza has been limited by the paucity of available drugs, the short duration of symptoms in uncomplicated influenza, and the changing patterns of drug resistance in influenza viral strains. In the past, influenza A infection could be treated with the M-2 channel blockers amantadine and rimantadine. Widespread resistance has currently relegated these compounds to historical interest only. Neuraminidase inhibitors have been the mainstay for treatment of influenza A and B viruses for many years. As their name implies, these drugs inhibit the influenza neuraminidase and thus limit the egress of influenza virus from an infected cell. They are most effective in patients whose influenza illness is recognized early and confirmed by rapid diagnostic testing or on the basis of clinical and epidemiologic evidence. In experimental trials, these drugs hasten the resolution of symptoms if given within 48 h of infection. There are indications for their use both prophylactically—either throughout the season or, when a case is recognized in a close contact, in the short term—and therapeutically. The anticipated effect of early administration is the resolution of symptoms 1–2 days sooner than without treatment. The use of neuraminidase inhibitors is recommended for complicated influenza infections in hospitalized patients in the absence of formal proof of efficacy and when diagnosis may have been delayed. All the available neuraminidase inhibitors carry a risk of development of resistance, particularly with prolonged administration (e.g., to an immunodeficient individual with persistent recovery of influenza virus). Resistance to neuraminidase inhibitors is not widespread among currently circulating influenza A or B strains, but its development has been demonstrated in the laboratory, and clinical resistance could influence the utility of these drugs. The defined risk groups who can benefit from neuraminidase inhibitors include children <2 years of age, adults >65 years of age,

patients with chronic conditions, immunosuppressed individuals, pregnant women, women who have delivered infants  $\leq 2$  weeks previously, patients  $< 19$  years old who are receiving long-term aspirin

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