PREVENTION

Live vaccines have been developed against adenovirus types 4 and 7 and have been highly efficacious in control of acute respiratory disease among military recruits. These vaccines consist of live, unattenuated virus administered in enteric-coated capsules. Infection of the gastrointestinal tract with types 4 and 7 does not cause disease but stimulates local and systemic antibodies that are protective against subsequent acute respiratory disease due to those serotypes. These vaccines were not produced from 1999 to 2011 but are now available again and are being used effectively in military recruits. Adenoviruses are also being studied as live-virus vectors for the delivery of vaccine antigens and for gene therapy.

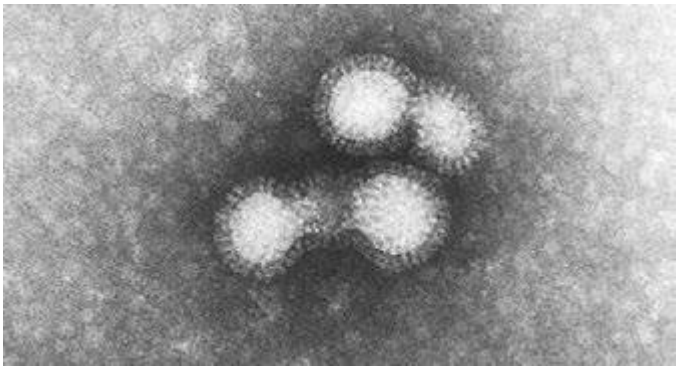

FIGURE 224-1 **An electron micrograph** of influenza A virus (×40,000).

224 Influenza

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DEFINITION

Influenza is an acute respiratory illness caused by infection with influenza viruses. The illness affects the upper and/or lower respiratory tract and is often accompanied by systemic signs and symptoms such as fever, headache, myalgia, and weakness. Outbreaks of illness of variable extent and severity occur nearly every year. Such outbreaks result in significant morbidity rates in the general population and in increased mortality rates among certain high-risk patients, mainly as a result of pulmonary complications.

ETIOLOGIC AGENT

Influenza viruses are members of the Orthomyxoviridae family, of which influenza A, B, and C viruses constitute three separate genera. The designation of influenza viruses as type A, B, or C is based on antigenic characteristics of the nucleoprotein (NP) and matrix (M) protein antigens. Influenza A viruses are further subdivided (subtyped) on the basis of the surface hemagglutinin (H) and neuraminidase (N) antigens; individual strains are designated according to the site of origin, isolate number, year of isolation, and subtype—for example, influenza A/California/07/2009 (H1N1). Influenza A has 18 distinct H subtypes and 11 distinct N subtypes, of which only H1, H2, H3, N1, and N2 have been associated with epidemics of disease in humans. Avian influenza A viruses have been associated with small outbreaks and sporadic cases in humans (see below). Influenza B and C viruses are designated similarly to influenza A viruses, but H and N antigens from these viruses do not receive subtype designations because intratypic variations in influenza B antigens are less extensive than those in influenza A viruses and may not occur with influenza C virus.

Influenza A and B viruses are major human pathogens and the most extensively studied of the Orthomyxoviridae. Type A and type B viruses are morphologically similar. The virions are irregularly shaped spherical particles, measure 80–120 nm in diameter, and have a lipid envelope from the surface of which the H and N glycoproteins project (Fig. 224-1). The hemagglutinin is the site by which the virus binds to sialic acid cell receptors, whereas the neuraminidase degrades the receptor and plays a role in the release of the virus from infected cells after replication has taken place. Influenza viruses enter cells by receptor-mediated endocytosis, forming a virus-containing endosome. The viral hemagglutinin mediates fusion of the endosomal membrane with the virus envelope, and viral nucleocapsids are subsequently released into the cytoplasm. Immune responses to the H antigen are the major determinants of protection against infection with influenza virus, whereas those to the N antigen limit viral spread and contribute to reduction of the infection. The lipid envelope of influenza A virus also contains the M proteins M1 and M2, which are involved in stabilization of the lipid envelope and in virus assembly. The virion also contains the NP antigen, which is associated with the viral genome, as well as three polymerase (P) proteins that are essential for transcription and synthesis of viral RNA. Two nonstructural proteins function as an interferon antagonist and posttranscriptional regulator (NS1) and a nuclear export factor (NS2 or NEP).

The genomes of influenza A and B viruses consist of eight single-strand RNA segments, which code for the structural and nonstructural proteins. Because the genome is segmented, the opportunity for gene reassortment during infection is high; reassortment often takes place during infection of cells with more than one influenza A virus.

EPIDEMIOLOGY

Influenza outbreaks occur virtually every year, although their extent and severity vary widely. Localized outbreaks take place at variable intervals, usually every 1–3 years. Global pandemics have occurred at variable intervals, but much less frequently than interpandemic outbreaks (Table 224-1). The most recent pandemic emerged in March of 2009 and was caused by an influenza A/H1N1 virus that rapidly spread worldwide over the next several months.

Influenza A Virus • ***ANTIGENIC VARIATION AND INFLUENZA OUTBREAKS AND PANDEMICS*** The most extensive and severe outbreaks of influenza are caused by influenza A viruses, in part because of the remarkable propensity of the H and N antigens of these viruses to undergo periodic antigenic variation. Major antigenic variations, called *antigenic shifts*, are seen only with influenza A viruses and may be associated with pandemics. Minor variations are called *antigenic drifts*. Antigenic variation may involve the hemagglutinin alone or both the hemagglutinin and the neuraminidase. An example of an antigenic shift involving both the hemagglutinin and the neuraminidase is that of 1957, when the predominant influenza A virus subtype shifted from H1N1 to H2N2; this shift resulted in a severe pandemic, with an estimated 70,000 excess deaths (i.e., deaths in excess of the number expected without an influenza epidemic) in the United States alone. This excess mortality was significantly greater than that during interpandemic influenza seasons.

TABLE 224-1 EMERGENCE OF ANTIGENIC SUBTYPES OF INFLUENZA A VIRUS ASSOCIATED WITH PANDEMIC OR EPIDEMIC DISEASE

Years	Subtype	Extent of Outbreak
1889–1890	H2N8[a]	Severe pandemic
1900–1903	H3N8[a]	?Moderate epidemic
1918–1919	H1N1[b] (formerly HswN1)	Severe pandemic
1933–1935	H1N1[b] (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

[a] As determined by retrospective serologic survey of individuals alive during those years ("seroarchaeology"). [b] Hemagglutinins formerly designated as Hsw and H0 are now classified as variants of H1. [c] From this time until 2008–2009, viruses of the H1N1 and H3N2 subtypes circulated either in alternating years or concurrently. [d] A novel influenza A/H1N1 virus emerged to cause this pandemic.