CNS side effects, primarily jitteriness, anxiety, insomnia, or difficulty concentrating. These side effects disappear promptly upon cessation of therapy. Rimantadine appears to be equally efficacious and is associated with less frequent CNS side effects than is amantadine.

Ribavirin is a nucleoside analogue with activity against influenza A and B viruses in vitro. Its efficacy against influenza when administered as an aerosol is reportedly variable, and it is ineffective when administered orally. Its efficacy in the treatment of influenza A or B has not been established.

The therapeutic efficacy of antiviral compounds in influenza has been demonstrated primarily in studies of young adults with uncomplicated disease. The effectiveness of these drugs in the treatment or prevention of complications of influenza is unclear. Pooled analyses of observational investigations and some efficacy studies have suggested that treatment with oseltamivir may reduce the frequency of lower respiratory complications and hospitalization. Therapy for primary influenza pneumonia is directed at maintaining oxygenation and is most appropriately undertaken in an intensive care unit, with aggressive respiratory and hemodynamic support as needed.

Antibacterial drugs should be reserved for the treatment of bacterial complications of acute influenza, such as secondary bacterial pneumonia. The choice of antibiotics should be guided by Gram's staining and culture of appropriate specimens of respiratory secretions, such as sputum. If the etiology of a case of bacterial pneumonia is unclear from an examination of respiratory secretions, empirical antibiotics effective against the most common bacterial pathogens in this setting (*S. pneumoniae*, *S. aureus*, and *H. influenzae*) should be selected **(Chaps. 171, 172, and 182)**.

For uncomplicated influenza in individuals at low risk of complications, symptom-based rather than antiviral therapy may be considered. Acetaminophen or nonsteroidal anti-inflammatory agents can be used for relief of headache, myalgia, and fever, but salicylates should be avoided in children <18 years of age because of the possible association with Reye's syndrome (see "Extrapulmonary Complications," above). Because cough is ordinarily self-limited, treatment with cough suppressants generally is not indicated; codeine-containing compounds may be used if the cough is particularly troublesome. Patients should be advised to rest and maintain hydration during acute illness and to return to full activity only gradually after illness has resolved, especially if it has been severe.

PROPHYLAXIS

The major public health measure for prevention of influenza is vaccination. Both inactivated (killed) and live attenuated vaccines are available and are generated from isolates of influenza A and B viruses that circulated in the previous influenza seasons and are anticipated to circulate in the upcoming season. For inactivated vaccines, 50–80% protection against influenza is expected if the vaccine virus and the currently circulating viruses are closely related. Available inactivated vaccines have been highly purified and are associated with few reactions. Up to 5% of individuals experience low-grade fever and mild systemic symptoms 8–24 h after vaccination, and up to one-third develop mild redness or tenderness at the vaccination site. Although the 1976 swine influenza vaccine appears to have been associated with an increased frequency of Guillain-Barré syndrome, influenza vaccines administered since 1976 generally have not been. Possible exceptions were noted during the 1992–1993 and 1993–1994 influenza seasons, when there may have been an excess risk of this syndrome (slightly more than 1 case per 1 million vaccine recipients). Large-scale studies of vaccination with the 2009 pandemic H1N1 vaccine also suggested a possible increased risk of Guillain-Barré syndrome (1 case per 1 million vaccinees). However, the overall health risk following influenza substantially outweighs the potential risk associated with vaccination.

A live attenuated influenza vaccine administered by intranasal spray is available. The vaccine is generated by reassortment between currently circulating strains of influenza A and B viruses and a cold-adapted, attenuated master strain. The cold-adapted vaccine is well tolerated and highly efficacious (>90% protective) in young children; in one study, it provided protection against a circulating influenza virus that had drifted antigenically away from the vaccine strain. Live attenuated vaccine is approved for use in healthy nonpregnant persons 2–49 years of age.

Since 1975, influenza vaccines have been trivalent—i.e., they have contained two influenza A subtypes (H3N2 and H1N1) and one influenza B component. However, two antigenically distinct lineages of influenza B virus have circulated since the 1980s, and a quadrivalent vaccine that includes both B lineages is now available (2013–2014) as well. Quadrivalent vaccines are available in both inactivated and live-attenuated vaccine formulations.

Inactivated influenza vaccines have been noted to be less immunogenic in the elderly. A higher-dose trivalent vaccine containing 60 μg of each antigen and a lower-dose, intradermally administered trivalent vaccine containing 9 μg of each antigen have been approved for use in individuals ≥65 years of age and individuals 18–64 years of age, respectively.

The influenza vaccines discussed above are manufactured in eggs and should not be administered to persons with true hypersensitivity to eggs. For use in this situation, an egg-free vaccine manufactured in cells through recombinant DNA techniques (Flublok®; Protein Sciences Corporation, Meriden, CT) has been approved. Active research is under way to develop vaccines with broad activity against antigenically distinct subtypes ("universal influenza vaccines").

Historically, the U.S. Public Health Service has recommended influenza vaccination for certain groups at high risk for complications of influenza on the basis of age or underlying disease (Table 224-2) or for their close contacts. Although such individuals will continue to be the focus of vaccination programs, the recommendations have been progressively expanded, and immunization of the entire population above the age of 6 months has been recommended since 2010–2011. (Approved influenza vaccines are not available for infants <6 months of age.) This expanded recommendation reflects increased recognition of previously unappreciated risk factors (e.g., obesity, postpartum conditions, and racial or ethnic influences) as well as an appreciation that more widespread use of vaccine is required for influenza control. Inactivated vaccines may be administered safely to immunocompromised patients. Influenza vaccination is not associated with exacerbations of chronic nervous system diseases such as multiple sclerosis. Vaccine should be administered early in the autumn before influenza outbreaks occur and should then be given annually to maintain immunity against the most current influenza virus strains.

Although antiviral drugs provide chemoprophylaxis against influenza, their use for that purpose has been limited because of concern about current and future development of resistance. Chemoprophylaxis with oseltamivir or zanamivir has been 84–89% efficacious against influenza A and B (Table 224-3). Chemoprophylaxis with amantadine or rimantadine is no longer recommended because of widespread resistance to these drugs. In earlier studies with sensitive viruses, prophylaxis with amantadine or rimantadine was 70–100% effective against illness associated with influenza A virus.

Chemoprophylaxis for healthy persons after community exposure generally is not recommended but may be considered for individuals at high risk of complications who have had close contact with an acutely ill person with influenza. During an outbreak, antiviral chemoprophylaxis can be administered simultaneously with inactivated vaccine because the drugs do not interfere with an immune response to the vaccine. However, concurrent administration of chemoprophylaxis and live attenuated vaccine may interfere with the immune response to the latter. Antiviral drugs should not be administered until at least 2 weeks after administration of live vaccine, and administration of live vaccine should not begin until at least 48 h after antiviral drug administration has been stopped. Chemoprophylaxis may also be considered to control nosocomial outbreaks of influenza. For that purpose, prophylaxis should be instituted promptly when influenza activity is detected and must be continued daily for the duration of the outbreak.