

## Influenza Virus Vaccine Inactivated (Seasonal)

### Vaccines 80:12 (AHFS primary); im100 (VA primary)

■ Influenza virus vaccine inactivated stimulates active immunity to influenza virus infection. There are 2 types of influenza virus vaccines commercially available in the US for prevention of seasonal influenza: influenza virus vaccine inactivated and influenza virus vaccine live intranasal. Seasonal inactivated influenza virus vaccines are trivalent vaccines containing noninfectious, suitably inactivated influenza virus types A and B subunits and are administered IM; seasonal influenza virus vaccine live intranasal is a trivalent vaccine containing live, attenuated (cold-adapted) influenza virus types A and B and is administered intranasally. (For information on the intranasal seasonal influenza vaccine, see Influenza Virus Vaccine Live Intranasal (Seasonal) 80:12.)

### Uses

Influenza virus vaccine inactivated is used to stimulate active immunity to influenza virus strains contained in the vaccine for the prevention of seasonal influenza.

Annual vaccination against influenza is the most effective strategy for preventing seasonal influenza virus infection and its complications. Unless contraindicated, the US Public Health Service Advisory Committee on Immunization Practices (ACIP) recommends annual influenza vaccination against seasonal influenza in all adults 50 years of age or older (and other adults who want to reduce their risk of becoming ill with influenza or transmitting influenza to others), all adolescents, and all children 6 months of age or older. Vaccination against seasonal influenza is recommended for otherwise healthy individuals as well as those who have medical conditions that put them at increased risk for influenza-related complications.

ACIP Recommends Annual Vaccination Against Seasonal Influenza for the Following Individuals Using an Appropriate Vaccine:

- All adults 50 years of age or older
- Adults who want to reduce their risk of becoming ill with influenza or transmitting influenza to others
- All children and adolescents 6 months to 18 years of age
- Children and adolescents 6 months to 18 years of age receiving long-term aspirin therapy who might therefore be at risk for Reye's syndrome after influenza infection
- Women who will be pregnant during the influenza season
- Children, adolescents, and adults with chronic pulmonary (including asthma), cardiovascular (except hypertension), renal, hepatic, cognitive, neurologic/neuromuscular, hematologic, or metabolic disorders (including diabetes mellitus)
- Children, adolescents, and adults who are immunosuppressed, including those receiving immunosuppressive drugs and those with human immunodeficiency virus (HIV) infection
- Children, adolescents, or adults who are residents of nursing homes and other chronic-care facilities
- Health-care workers
- Household contacts (including children) and caregivers of children younger than 5 years of age (especially contacts of infants younger than 6 months of age)
- Household contacts (including children) and caregivers of adults 50 years of age or older
- Household contacts (including children) and caregivers of individuals with medical conditions that put them at high risk for severe influenza complications

Seasonal influenza vaccines are formulated annually to contain influenza A and B antigens predicted to represent strains of influenza virus likely to circulate in the US during the upcoming influenza season. The vaccines are not effective against all possible strains of influenza virus and provide protection only against those strains of virus from which the vaccine is prepared as well as against closely related strains. Efficacy (i.e., prevention of illness among vaccinated individuals in controlled trials) and effectiveness (i.e., prevention of illness in vaccinated populations) of seasonal influenza vaccines depend in part on the age and immunocompetence of the vaccine recipient and the degree of similarity between the virus strains in the vaccine and circulating strains.

Seasonal influenza vaccines for the 2009–2010 influenza season are *not* expected to provide protection against infection with the 2009 pandemic influenza A (H1N1) virus, previously referred to as the novel 2009 influenza A (H1N1) virus or swine-origin influenza A (H1N1) virus. However, influenza A (H1N1) 2009 monovalent vaccine may be indicated in certain groups at highest risk for infection or influenza-related complications to prevent infection caused by this strain. Seasonal influenza vaccines also are *not* expected to provide protection against infection with avian influenza A viruses, including avian influenza A (H5N1). Although an inactivated influenza A (H5N1) monovalent vaccine has been approved by the US Food and Drug Administration (FDA), the vaccine is not available commercially but has been purchased by the US Federal Government for inclusion in the National Stockpile.

Seasonal influenza virus vaccine 2009–2010 was formulated based on specifications of the FDA's Vaccines and Related Biological Products Advisory Committee (VRBPAC) to contain antigens representative of the strains of influenza A (H3N2), influenza A (H1N1), and influenza B viruses likely to circulate in the US during the 2009–2010 influenza season. (See Composition of 2009–2010 Influenza Virus Vaccine Inactivated under Chemistry and Stability: Chemistry.) Only 1 of 3 antigens contained in the 2009–2010 seasonal influenza vaccine (the influenza type B component) differs from the antigens contained in the 2008–2009 seasonal influenza vaccine.

Immunity declines in the year following influenza vaccination; therefore, a history of vaccination against seasonal influenza in any previous year does not preclude the need for vaccination with the current seasonal vaccine for the upcoming influenza season. In addition, although major antigenic shifts in influenza viruses are uncommon (as opposed to drifts, which are common), protection afforded by a history of vaccination in recent years would be particularly unlikely when such major changes in antigenic subtype of the virus occur.

Information regarding influenza surveillance and updated recommendations for prevention and treatment of seasonal influenza is available from the Centers for Disease Control and Prevention (CDC) at <http://www.cdc.gov/flu>. CDC information regarding prevention and treatment of 2009 influenza A (H1N1) is available at <http://www.cdc.gov/h1n1flu> and information regarding avian influenza A (H5N1) is available at <http://www.cdc.gov/flu/avian>.

### ■ Choice of Influenza Vaccines for Prevention of Seasonal Influenza

There are 2 different types of influenza virus vaccines commercially available in the US for active immunization against seasonal influenza: influenza virus vaccine inactivated and influenza virus vaccine live intranasal. Seasonal influenza virus vaccine inactivated contains inactivated virus subunits (split virus or subvirion) and is administered IM. Seasonal influenza virus vaccine live intranasal contains attenuated, live virus reassortants and is given intranasally. Both vaccine types are reformulated each year to contain strains of influenza virus antigenically equivalent to strains likely to circulate in the US during the upcoming influenza season and one of these vaccines must be administered annually to provide optimal protection against seasonal influenza infection.

There is evidence that influenza virus vaccine inactivated and influenza virus vaccine live intranasal are similarly effective in preventing seasonal influenza. The parenteral influenza virus vaccine inactivated has several advantages since it can be used in some individuals who should not receive influenza virus vaccine live intranasal, including infants 6–23 months of age, adults 50 years of age or older, pregnant women, individuals with underlying medical conditions that may predispose them to severe disease following influenza infection, children and adolescents receiving long-term aspirin therapy, individuals receiving immunosuppressive therapy, and individuals who have close contact with severely immunocompromised individuals requiring a protective environment (e.g., hematopoietic stem cell transplant recipients [HSCT]).

The ACIP states that either influenza virus vaccine inactivated or influenza virus vaccine live intranasal can be used for prevention of seasonal influenza in healthy, non-pregnant individuals 2–49 years of age (including those who wish to reduce the likelihood of becoming ill with influenza or transmitting influenza to others), health-care workers, those who are in close contact with groups at high risk of influenza, and those who are in close contact with less severely immunocompromised individuals (e.g., those not requiring a protective environment, those with diabetes or HIV infection, asthma patients taking corticosteroids). Possible advantages of the intranasal vaccine over influenza virus vaccine inactivated in such individuals include its potential to induce a broad mucosal and systemic immune response, ease of administration, and improved acceptance of intranasal rather than IM administration; possible disadvantages include age restrictions (cannot be used in children younger than 2 years of age or adults 50 years of age or older) and the risk that the live vaccine virus could be transmitted from the vaccinee to close contacts who are severely immunocompromised. During periods when seasonal influenza virus vaccine inactivated is in short supply, use of influenza virus vaccine live intranasal is encouraged for eligible individuals.

Fluzone<sup>®</sup> influenza virus vaccine inactivated 2009–2010 may be used in adults, adolescents, and children 6 months of age or older. Fluvirin<sup>®</sup> influenza virus vaccine inactivated 2009–2010 may be used in adults, adolescents, and children 4 years of age or older. Afluria<sup>®</sup>, Fluairix<sup>®</sup>, and FluLaval<sup>®</sup> influenza virus vaccine inactivated 2009–2010 are used only in adults 18 years of age or older.

### ■ Management of Exposure

Management of influenza exposure includes preventive and control measures that involve vaccination programs and treatment or prophylaxis with appropriate antivirals. (See Adjunctive Use of Antiviral Agents under Uses: Management of Exposure.)

In some individuals, influenza can exacerbate underlying medical conditions (e.g., pulmonary or cardiac diseases), lead to secondary bacterial pneumonia, sinusitis, otitis media, or primary influenza viral pneumonia, or occur as part of a coinfection with other viral or bacterial pathogens. Influenza infection also has been associated with encephalopathy, transverse myelitis, Reye's syndrome, myositis, myocarditis, and pericarditis. The risks for influenza-related complications, hospitalizations, and death are increased in geriatric adults 65 years of age or older, children younger than 2 years of age, and individuals of any age with certain underlying medical conditions. Even in individuals not at such increased risk for complications, influenza illness can result in absenteeism, disruption in work and provided services (e.g., in health-care providers, in others providing essential community services), and decreased productivity as well as associated health-care costs.

Excess hospitalizations and deaths attributable to pneumonia and influenza occur in a substantial number of individuals in the US during influenza epidemics. During influenza epidemics from 1979–1980 to 2000–2001, the estimated influenza-associated hospitalization rates averaged 226,000 per year (55,000 to 431,000 per epidemic), with the greatest numbers of such hospitalizations occurring during epidemics caused by type A (H3N2) viruses. In the US, approximately 19,000 influenza-associated pulmonary and

circulatory deaths were estimated to occur during each influenza season in the period of 1976–1990, compared with approximately 36,000 deaths during 1990–1999. Geriatric adults with underlying chronic lung disease are at particular risk for hospitalizations and deaths attributable to pneumonia and influenza, and older adults account for at least 90% of deaths attributed to pneumonia and influenza.

Vaccination with seasonal influenza vaccine *before* the influenza season is the single most effective means for preventing or attenuating influenza in individuals at highest risk of influenza-related complications and is the principal measure for controlling the impact of the disease. However, because of the risks of waning immunity during the season and potential antigenic variations of the virus from year to year, the timing of seasonal influenza vaccination programs and vaccine formulation employed are important considerations. (See Timing of Influenza Vaccination under Uses: Management of Exposure.)

### **Target Groups for Vaccination Efforts**

The ACIP, the Canadian National Advisory Committee on Immunization (NACI), and others recommend that seasonal influenza vaccination efforts target individuals at higher risk of influenza or influenza-related complications and those who live with or care for such individuals.

Despite recognition that optimum medical care includes regular review of immunization records and appropriately scheduled immunization for both adults and children, a substantial number of individuals considered at risk for influenza-associated complications do not receive the seasonal influenza vaccine each year. The national health objective for the year 2010 is to achieve vaccination coverage for 90% of geriatric adults 65 years of age or older and 90% of nursing home residents. Despite gains in seasonal influenza vaccination rates, optimal levels remain to be achieved in all areas of the US and in certain groups (e.g., Hispanics, non-Hispanic blacks). Data from the 2006–2007 influenza season indicate that 36% of adults 50–64 years of age and 66% of adults 65 years of age or older received the vaccine. In those with chronic medical conditions that put them at high risk of influenza-related complications, 25.5% of those 18–49 years of age and 46.1% of those 50–64 years of age were vaccinated. Special emphasis should be placed on promoting annual influenza vaccination among geriatric individuals with additional risk, particularly those with an underlying cardiopulmonary disease, and on reducing racial and ethnic health disparities. Data from 2007 indicate that estimated vaccination coverage among individuals 65 years of age or older were 70% for non-Hispanic whites, 58% for non-Hispanic blacks, and 54% for Hispanics.

Staff in facilities providing ongoing medical care (e.g., physicians' offices, public health clinics, outpatient clinics, employee health clinics, hemodialysis centers, hospital specialty-care clinics, managed-care settings, outpatient rehabilitation programs) should identify and mark the medical records of individuals for whom vaccination against seasonal influenza virus is recommended. ACIP recommends that the seasonal vaccine then be offered to these individuals during visits throughout the influenza season; the offer of vaccine and its receipt or refusal should be documented in each individual's medical record. Individuals in high-risk groups who do not have regularly scheduled visits during the fall should be reminded by mail, telephone, or other means of the need for vaccination.

#### **Health-care Workers.**

ACIP and the Healthcare Infection Control Practices Advisory Committee (HICPAC) recommend routine annual vaccination against seasonal influenza for all health-care workers, unless contraindicated.

Beginning in January 2007, the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) began requiring hospitals and long-term care facilities to offer seasonal influenza vaccination to staff, volunteers, and licensed independent practitioners. A number of professional organizations, including the American Society of Health-System Pharmacists (ASHP), the American Academy of Pediatrics (AAP), and the Infectious Diseases Society of America (IDSA), support vaccination of health-care workers against seasonal influenza.

Influenza vaccination of health-care workers is considered a high priority since it reduces morbidity associated with seasonal influenza in health-care settings and has been associated with reduced work absenteeism and fewer deaths in nursing home patients and elderly hospitalized patients. Low vaccination rates among health-care workers have been associated with influenza outbreaks in hospitals and long-term care facilities and higher vaccination levels among staff have been associated with a lower incidence of nosocomial influenza. Data from the 2005–2006 influenza season indicate that vaccination coverage among health-care workers was only 42%. One of the national health objectives for the year 2010 is to achieve vaccination coverage rates of 60% in health-care workers.

Annual vaccination against seasonal influenza is recommended for physicians, nurses, and other personnel in both hospital and outpatient care settings (including medical emergency response workers such as paramedics and emergency medical technicians), employees of nursing homes and chronic-care facilities who have contact with patients or residents, and students in these professions who will have contact with patients. Facilities that employ health-care workers are strongly encouraged to provide easily accessible influenza education and vaccination programs for all staff (including all full-time, part-time, and temporary staff) with particular emphasis on workers who provide direct care to individuals at high risk for influenza complications. HICPAC suggests that the optimal time to provide organized vaccination programs for health-care workers is during October and November; however, seasonal influenza vaccine still should be offered to unvaccinated workers throughout the influenza season, even after influenza activity has been documented in the community.

#### **Individuals with Chronic Medical Conditions.**

Individuals with chronic medical conditions that increase the risk of influenza or influenza-related complications should receive annual vaccination against seasonal influenza.

Groups considered to be at increased risk for influenza-related complications include adults, adolescents, and children with chronic disorders of the cardiovascular (except hypertension) and/or pulmonary systems (e.g., acquired or congenital heart disease, cystic fibrosis, chronic asthma, tuberculosis, bronchopulmonary dysplasia), spinal cord injuries, seizure disorders, other neuromuscular disorders), and residents of nursing homes and other chronic-care facilities housing patients of any age with chronic medical conditions. Other groups considered at increased risk of influenza-related complications include adults, adolescents, and children who have chronic metabolic diseases (including diabetes mellitus), renal or hepatic dysfunction, hematologic disorders (e.g., hemoglobinopathies), or immunosuppression (including those immunosuppressed because of immunosuppressive therapy or HIV infection) and children and adolescents 6 months through 18 years of age who are receiving long-term aspirin therapy and therefore may be at risk of developing Reye's syndrome following influenza infection.

The risk of complications following influenza infection also may be increased in patients who have undergone allogeneic bone marrow transplantation or hematopoietic stem cell transplantation (HSCT) and vaccination of such individuals also should be considered. (See Hematopoietic Stem Cell Transplant Recipients under Management of Exposure: Target Groups for Vaccination Efforts, in Uses.)

For information on influenza risk and vaccination recommendations in HIV-infected individuals, see HIV-infected Individuals under Management of Exposure: Target Groups for Vaccination Efforts, in Uses.

#### **Adults 50–64 Years of Age.**

Routine annual vaccination against seasonal influenza is recommended for all adults 50 years of age or older because this group of adults has an increased prevalence of high-risk conditions. ACIP recommends that facilities providing services to adults 50 years of age or older (e.g., assisted living housing, retirement communities, recreation centers) offer residents, attendees, and staff annual on-site vaccination before the start of the influenza season and continue to offer the seasonal influenza vaccine to unvaccinated individuals throughout the fall and winter.

Based on the National Health Interview Survey (NHIS), the estimated national influenza vaccine coverage among persons 50–64 years of age increased slightly from 31.6% in the 2005–2006 influenza season to 36% in the 2006–2007 season and 38.4% in the 2007–2008 influenza season. Individuals 50–64 years of age with underlying medical conditions are at a substantially increased risk for hospitalizations during influenza season compared with healthy adults in this age group. Vaccination of healthy adults 50–64 years of age can reduce the number of illnesses, clinician visits, work absenteeism, anti-infective use, and decrease use of health-care resources.

#### **Geriatric Adults.**

Geriatric adults 65 years of age or older should receive routine annual vaccination against seasonal influenza.

About 90% or more of influenza-associated deaths occur in adults 65 years of age and older, and the influenza-associated fatality rate in this age group during 6 epidemics from 1972–1982 was 34–104 times that in younger individuals. The risk increases with age in this population, and those 85 years of age or older are 16 times more likely than those 65–69 years of age to die of an influenza-associated underlying pneumonia and influenza death. During 1990–1999, estimated average rates of influenza-associated pulmonary and circulatory deaths were 98.3 per 100,000 persons among geriatric adults 65 years of age or older. The risk of hospitalization and death attributable to pneumonia and influenza is particularly increased for geriatric adults with underlying chronic lung disease compared with those who do not have an underlying pulmonary condition. A retrospective analysis during 1996–2000 estimated that the risk during influenza season among persons 65 years of age or older with underlying conditions and at risk for influenza-related complications (i.e., one or more of the conditions listed as indications for vaccination) was approximately 560 influenza-associated hospitalizations per 100,000 persons, compared with approximately 190 per 100,000 in healthy elderly persons. Shifts in age distribution in the US population probably will increase the need for health-care services and effective preventive strategies aimed against respiratory infectious diseases. Therefore, targeting geriatric individuals for annual influenza vaccination is particularly important. Among community-dwelling adults 65 years of age or older with and without high-risk medical conditions (e.g., heart disease and diabetes), influenza vaccination reduces the frequency of secondary complications and reduces the risk for influenza-related hospitalization and death.

Based on NHIS results, the estimated national influenza vaccine coverage among persons 65 years of age or older increased only slightly from 64.5% in the 2005–2006 influenza season to 66% in the 2006–2007 season and 66.3% in the 2007–2008 influenza season.

#### **Children 6 Months to 4 Years of Age.**

Data from several studies indicate that hospitalization rates are higher in young children than among older children when influenza viruses are circulating, and that these increased rates are comparable to those for other high-risk groups.

ACIP recommends that all children 6 months to 4 years (59 months) of age receive annual vaccination against seasonal influenza. Beginning in the 2004–2005 influenza season, ACIP first recommended that infants 6–23 months of age be targeted for annual influenza vaccination based on an increased risk of influenza-associated hospitalizations in infants 23 months of age or younger. Then, in the 2006–2007 season, the ACIP

expanded these recommendations to also include children 24–59 months of age. ACIP continues to recommend seasonal influenza vaccination in children 6 months of age or older who have high-risk medical conditions. Influenza virus vaccine inactivated is not labeled for use in children younger than 6 months of age, the pediatric group at greatest risk for influenza-related complications; vaccinating household contacts and other close contacts might reduce the incidence of seasonal influenza in these children. Therefore, ACIP encourages vaccination against seasonal influenza in individuals who are close contacts of children 0–59 months of age.

The Vaccines for Children (VFC) program provides all routine childhood vaccines recommended by ACIP, including seasonal influenza vaccine, to VFC-eligible children. Detailed information about the VFC program is available at <http://www.cdc.gov/vaccines/programs/vfc/default.htm>.

#### **Children and Adolescents 5–18 Years of Age.**

Beginning in the 2008–2009 influenza season, ACIP recommended that all children 5–18 years of age receive annual vaccination against seasonal influenza. This recommendation to expand routine influenza vaccination to include all school-age children and adolescents 5–18 years of age was based on accumulated evidence that influenza vaccine is effective and safe for school-aged children, increased evidence that seasonal influenza has substantial adverse impacts among school-aged children and their contacts (e.g., school absenteeism, increased anti-infective use, healthcare visits, parental work loss), and an expectation that a simplified age-based influenza vaccine recommendation for all school-age children and adolescents will improve vaccine coverage levels among the approximately 50% of school-aged children who already had a risk- or contact-based indication for annual influenza vaccination. More than 8 million children and adolescents in the US (including 2.2 million individuals 10–18 years of age with asthma) have at least one medical condition that places them at high risk for complications following influenza infection. (See Individuals with Chronic Medical Conditions under Management of Exposure: Target Groups for Vaccination Efforts, in Uses.)

While high-risk children and adolescents should undergo annual vaccination against seasonal influenza, few in the pediatric age group actually receive the vaccine each year. Therefore, children and adolescents at risk should be targeted for organized seasonal influenza vaccination programs. The AAP recommends that clinicians increase their efforts through tracking and recall systems to ensure that children and adolescents traditionally considered at high risk of severe influenza and influenza complications receive annual vaccination against seasonal influenza. These include children and adolescents with asthma or other chronic pulmonary disease (e.g., cystic fibrosis), hemodynamically significant cardiac disease, immunosuppressive disorders or therapy, HIV infection, sickle cell anemia and other hemoglobinopathies, disease requiring long-term aspirin therapy (e.g., rheumatoid arthritis, Kawasaki syndrome), chronic renal dysfunction, chronic metabolic disease (e.g., diabetes mellitus), or disorders that may impede adequate respiration (e.g., cognitive dysfunction, spinal cord injuries, seizure disorders, other neuromuscular disorders). (See Individuals with Chronic Medical Conditions under Management of Exposure: Target Groups for Vaccination Efforts, in Uses.)

Children and adolescents who have close contact (i.e., live, work, or otherwise are frequently in close proximity) with individuals at high risk for influenza-associated complications, including children 0–59 months of age, also should receive seasonal influenza virus vaccine. In addition, the vaccine may be administered to any child or adolescent 6 months of age or older (including those with no underlying medical condition) to reduce the likelihood of acquiring seasonal influenza. One study reported vaccine efficacy against laboratory-confirmed influenza illness of 56% among healthy children 3–9 years of age and 100% among healthy children and adolescents 10–18 years of age.

Some evidence suggests that influenza vaccination can effectively reduce the rate of otitis media and the use of anti-infectives in children. In one study in children 1–3 years of age who attended a day-care center, the frequency of acute otitis media associated with influenza A infection was 83% lower in influenza-vaccinated (with a trivalent formulation) versus unvaccinated children, and the overall frequency of otitis media was 35% lower in the vaccinated children, regardless of the presence of influenza infection; there was no difference in the frequency of respiratory tract infections. Randomization was by day-care center, and the study was unblinded and did not include a placebo control. In another study in children 15–71 months of age who received live attenuated (cold-adapted), trivalent influenza virus vaccine intranasally, the incidence of febrile otitis media was 30% lower in vaccinees than in placebo recipients. However, a large study conducted among children with a mean age of 14 months indicated that inactivated influenza vaccine was not effective against acute otitis media. ACIP states that influenza vaccine effectiveness against acute otitis media is not typically diagnosed using influenza virus culture and would be expected to be relatively low when assessing a nonspecific clinical outcome.

#### **Pregnant Women.**

Because pregnant women are at risk for influenza-related complications, ACIP recommends that all women who are pregnant or will be pregnant during the influenza season receive influenza virus vaccine inactivated for prevention of seasonal influenza. This includes pregnant women without underlying influenza risk factors. The American College of Obstetricians and Gynecologists (ACOG), AAP, American Academy of Family Physicians (AAFP), American College of Physicians (ACP), National Institutes of Health (NIH), IDSA, and other experts also recommend that pregnant women be

vaccinated against seasonal influenza with influenza virus vaccine inactivated. (See Cautions: Pregnancy, Fertility, and Lactation.)

Excess mortality associated with influenza among pregnant women was documented during the 1918–1919 and 1957–1958 pandemics. Case reports and limited studies indicate that pregnant women, including those without underlying risk factors, are at increased risk for serious influenza complications. Limited information is available on use of influenza virus vaccine inactivated in pregnant women. Data on safety of influenza virus vaccine live intranasal in pregnant women is not available.

#### **Contacts of High-risk Individuals.**

Individuals with clinical or subclinical influenza infection can transmit the infection to high-risk individuals. Preventing transmission of influenza from caregivers and household contacts to high-risk individuals might reduce influenza-related deaths in high-risk individuals. In addition to health-care workers, others who should be vaccinated because they can transmit influenza to high-risk individuals include employees of nursing homes and chronic-care facilities; employees of assisted living and other residences for high-risk individuals; individuals (e.g., visiting nurses, volunteer workers) who provide home care to high-risk individuals; crews on ships that cater to high-risk individuals; and all household contacts (including children 6 months of age or older) and out-of-home caregivers of individuals in high-risk groups.

Because children 59 months of age or younger are at increased risk for influenza-related health-care utilization, vaccination against seasonal influenza also is encouraged for their household contacts and out-of-home caretakers. Since influenza vaccines are not licensed by FDA for use in infants younger than 6 months of age, emphasis should be placed on vaccinating household or other contacts of infants younger than 6 months of age. ACIP states that when vaccine supply is limited, priority for vaccination should be given to contacts of infants in this age group.

#### **Residents of Nursing Homes and Other Chronic-care Facilities.**

The ACIP and others recommend routine annual vaccination against seasonal influenza for residents of nursing homes and other residential chronic-care facilities as soon as the vaccine is available. All residents should be vaccinated at one time immediately preceding the seasonal influenza season. Residents admitted through March after completion of seasonal vaccination program should be vaccinated at the time of admission. Since October 2005, the Centers for Medicare and Medicaid Services (CMS) has required nursing homes participating in the Medicare and Medicaid programs to offer all residents influenza and pneumococcal vaccines and to document the results. According to the requirements, each resident is to be vaccinated unless contraindicated medically, the resident or a legal representative refuses vaccination, or the vaccine is not available because of shortage.

#### **HIV-infected Individuals.**

Limited information is available concerning the frequency and severity of influenza illness or on the benefits of influenza vaccination in HIV-infected individuals. However, some reports suggest that symptoms of influenza illness may be prolonged and the risk for complications from influenza may be increased for some HIV-infected individuals. In addition, the risk for infections and complications caused by various other respiratory pathogens, including pneumococcal pneumonia and *Haemophilus influenzae* pneumonia (diseases that typically follow influenza in high-risk individuals), is increased in HIV-infected individuals.

The ACIP, AAP, NIH, and IDSA recommend annual vaccination against seasonal influenza for all HIV-infected adults, adolescents, and children 6 months of age or older since these individuals may be at high risk of complications from influenza. Influenza virus is not traditionally classified as an opportunistic pathogen, but many experts consider vaccination against the virus as logical in any HIV-infected individual (whether symptomatic or asymptomatic) because of the possible risks of respiratory infections in such patients and because some protection probably will be provided by the vaccine.

Although there is some evidence that influenza virus vaccine inactivated may transiently stimulate replication of HIV in some HIV-infected individuals, particularly those who are not receiving potent antiretroviral therapy (see HIV-infected Individuals under Response to Influenza Virus Vaccine Inactivated: Immunocompromised Individuals, in Pharmacology), and some clinicians have expressed concerns about the potential long-term consequences of possible resultant increases in viral load on the clinical status of HIV-infected individuals, there is no evidence of accelerated HIV disease progression in influenza-vaccinated patients. In addition, any transient increases in HIV replication that do occur appear to be associated with an effect on disease progression that is so minimal that it is difficult to detect.

Immunization against influenza may be less effective in individuals with HIV infection than in immunocompetent individuals since the antibody response to vaccines may be reduced and inversely correlated with the severity of the disease. There is evidence that influenza virus vaccine inactivated is highly effective in preventing symptomatic, laboratory-confirmed influenza infection among HIV-infected individuals with mean CD4<sup>+</sup> T-cell counts of 400/mm<sup>3</sup>; however, the vaccine may be less effective in those with more advanced disease and lower CD4<sup>+</sup> T-cell counts, especially those with counts less than 100/mm<sup>3</sup>. There is no evidence that a second dose of influenza vaccine improves the immune response in these individuals. (See HIV-infected Individuals under Response to Influenza Virus Vaccine Inactivated: Immunocompromised Individuals, in Pharmacology.)

Antiviral prophylaxis may be used in conjunction with, or as an alternative to, influenza virus vaccine inactivated in HIV-infected individuals who may have a poor antibody response to the vaccine and/or high risk of exposure to influenza A, especially

during influenza epidemics or institutional outbreaks. (See Adjunctive Use of Antiviral Agents under Uses: Management of Exposure.)

#### **Hematopoietic Stem Cell Transplant Recipients.**

Individuals who undergo hematopoietic stem cell transplant (HSCT) are at risk for a variety of opportunistic infections, including community-acquired respiratory viral infections (e.g., influenza, respiratory syncytial virus [RSV], parainfluenza virus, adenovirus). The CDC, IDSA, and American Society of Blood and Marrow Transplantation (ASBMT) have established guidelines for preventing opportunistic infections in HSCT recipients. These guidelines recommend life-long annual vaccination against seasonal influenza with influenza virus vaccine inactivated in all HSCT recipients who are 6 months of age or older. HSCT candidates should receive influenza virus vaccine inactivated the influenza season prior to HSCT and then annually thereafter, beginning 6 months or later after HSCT. The vaccine is not likely to be beneficial and is not recommended during the first 6 months after HSCT; antiviral prophylaxis can be used if community or nosocomial influenza outbreaks occur during this time period. If seasonal influenza outbreaks occur and it has been 6–24 months after HSCT or it has been longer than 24 months after HSCT and the patient is still substantially immunocompromised (i.e., receiving immunosuppressive therapy, having a relapse of the underlying disease, graft-versus-host disease [GVHD]), the HSCT recipient should immediately receive influenza virus vaccine inactivated if they have not yet received their annual seasonal vaccination. In addition, during influenza A outbreaks, the HSCT recipient can receive a regimen of antiviral prophylaxis to provide protection until antibody responses to the vaccine develop. (See Adjunctive Use of Antiviral Agents under Uses: Management of Exposure.)

The CDC, IDSA, and ASBMT guidelines also state that annual vaccination against seasonal influenza with influenza virus vaccine inactivated is strongly recommended for all family members and close or household contacts of HSCT recipients. Family members and close or household contacts should receive influenza virus vaccine inactivated beginning the influenza season before HSCT and annually thereafter for at least 24 months after HSCT. These contacts should continue to be vaccinated annually as long as the HSCT recipient is immunocompromised. Annual vaccination against seasonal influenza virus also is strongly recommended for all health-care workers of HSCT recipients. If a health-care worker, family member, or other close contact of an HSCT recipient receives influenza virus vaccine inactivated during an outbreak of seasonal influenza A, they also should receive a 2-week regimen of antiviral prophylaxis.

Recommendations for prevention of seasonal influenza virus infection in HSCT recipients are the same for both allogeneic and autologous transplants. The guidelines for preventing opportunistic infections among HSCT recipients published by the CDC, IDSA, and ASBMT should be consulted for additional information on preventing opportunistic infections in these patients (including vaccinations) and for information on hospital infection control, strategies for safe living after transplantation, and hematopoietic stem cell safety.

#### **Travelers.**

The risk of exposure to seasonal influenza during travel varies depending on the time of the year and destination. Influenza can occur throughout the year in tropical areas; the time of greatest influenza activity in the temperate regions of the southern hemisphere is from April through September. In temperate climate zones in the northern and southern hemispheres, travelers also can be exposed to influenza during the summer, especially when traveling in a organized tourist group that includes individuals from areas of the world where influenza viruses are circulating. Case clusters also have been reported among land and/or sea travelers in Alaska and the Yukon Territory during the summer months.

Because of the short incubation period for influenza infection (1–4 days), exposure to the virus during travel often will result in clinical illness that develops during travel; such illness may be an inconvenience or a potential danger, particularly for individuals at risk for influenza complications. In addition, travel may expose individuals to conditions that facilitate transmission of influenza. The CDC and ACIP recommend vaccination against seasonal influenza, preferably at least 2 weeks before departure, in individuals at high risk of influenza complications if they were not vaccinated during the previous fall or winter and they plan to travel to destinations or under circumstances where influenza is likely (e.g., travel to the tropics, travel with large organized travel groups at any time of the year, travel to the southern hemisphere from April through September). Although the efficacy of influenza immunization for travelers may vary depending on differences between influenza strains encountered during travel and those included in the current vaccine, there is insufficient evidence to advise in favor of or against revaccination of travelers who were vaccinated in the fall and who subsequently are traveling to areas where influenza may be circulating in the late spring and summer months. ACIP recommends that high-risk individuals who received the previous season's vaccine prior to travel be revaccinated during the fall or winter with the current seasonal vaccine.

Some clinicians recommend that all international *air* travelers be vaccinated against seasonal influenza regardless of the destination since the poor air circulation during such travel increases the risk of influenza transmission from an infected passenger. Immunization against seasonal influenza also has been recommended for the crew of cruise ships catering to passengers at high risk of influenza complications and for the high-risk passengers because the closed nature of this setting can facilitate influenza transmission. Although outbreaks of influenza have been reported among land and/or sea travelers in Alaska and the Yukon Territory during the summer, the CDC and Health

Canada state that special preventative measures currently are not recommended for otherwise healthy travelers to these areas; clinicians caring for patients presenting with febrile respiratory illness and/or pneumonia following recent travel to these areas should include influenza A in the differential diagnosis.

In addition to influenza virus subtypes that occur widely in humans, some travelers also may be at risk of exposure to avian influenza A. (See Travelers to Areas with Avian Influenza A under Uses: Avian Influenza A Virus Infection.)

#### **Individuals Providing Essential Services, Students, and Other Healthy Individuals.**

The ACIP and NACI state that individuals who provide essential community services should be considered for seasonal influenza vaccination programs to minimize possible disruption of essential activities, which could occur during influenza outbreaks. Students or other individuals in institutional settings (e.g., those who reside in dormitories) should be encouraged to participate in influenza vaccination programs to minimize the possible disruption of routine activities, which could occur during influenza outbreaks.

The ACIP, NACI, and others state that, depending on vaccine availability, influenza virus vaccine inactivated should be administered to any individual in the general population (adult, adolescent, or child 6 months of age and older) who wishes to reduce the likelihood of becoming ill with seasonal influenza (e.g., to reduce their chances of missing work or school as a consequence) or of transmitting influenza to others.

Influenza vaccine does not prevent influenza-like illness caused by infectious agents other than influenza, and many vaccinated individuals will still get such infections. Most cases of influenza-like illness are not caused by influenza, but by other viruses (e.g., rhinoviruses, respiratory syncytial virus [RSV], adenoviruses, parainfluenza viruses) or, less commonly, by bacteria (e.g., *Legionella*, *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, *Streptococcus pneumoniae*). Several patients with inhalational anthrax that occurred in the US during September and October 2001 in the context of bioterrorism-related exposures to anthrax spores presented with symptoms of influenza-like illness. Receipt of influenza vaccine will not definitely exclude influenza from the differential diagnosis of an influenza-like illness and will not increase the probability that other agents (including SARS coronavirus or *Bacillus anthracis*) are the cause of the illness. (For information on differential diagnosis of influenza-like illnesses, including inhalational anthrax, see Differential Diagnosis of Influenza and Influenza-like Illnesses under Uses: Treatment of Influenza A Virus Infections, in Amantadine Hydrochloride 8:18.04.)

There is some evidence that *selective* use of seasonal influenza virus vaccine inactivated in healthy, working-age adults can be a highly cost-effective strategy. Reductions in rates of illness (e.g., upper respiratory illness), sick leave (absenteeism), and clinician office visits have been reported in such adults who were vaccinated compared with those who were not, but substantial cost benefits may be limited to periods and circumstances associated with relatively high rates of symptomatic influenza infection. While it appears that substantial cost savings associated with routine immunization in such adults are less likely under most circumstances in the US, situations in which seasonal influenza vaccination programs can be seriously considered for healthy, working-age adults include those in which transmission of influenza to individuals at high risk could occur (e.g., in health-care workers), those in which the risk of an outbreak may be unusually high secondary to high population density and close proximity of workers to one another, and those in which high rates of absenteeism might disrupt severely a company's productivity or provision of essential services to the community. It also has been suggested that indirect cost benefits may result from vaccination of healthy, nongeriatric adults, who otherwise would be potential vectors of the disease, since any associated community decrease in the incidence of influenza would decrease the likelihood of exposure of high-risk individuals to the virus. Because the costs of the vaccine and time taken from work to be vaccinated importantly influence cost-effectiveness, any such seasonal vaccination program should be organized carefully to provide the vaccine conveniently and at the lowest possible cost.

#### **Timing of Influenza Vaccination**

Vaccination efforts against seasonal influenza should be structured to ensure vaccination of as many individuals as possible over the course of several months, with emphasis on vaccinating individuals before influenza activity begins in their community.

The optimal time to vaccinate against seasonal influenza in the US cannot be determined because influenza seasons vary in their timing and duration and more than one outbreak might occur in a single community in a single year. Vaccination efforts should begin as soon as seasonal vaccine is available (usually available beginning in September or October) and should be continued throughout the influenza season. Vaccine administered in December or later is likely to be beneficial, even if seasonal influenza activity has begun. To avoid missed opportunities for vaccination, providers should offer vaccination against seasonal influenza during routine health-care visits or during hospitalizations whenever vaccine is available.

Vaccination of children 6 months through 8 years of age who are receiving seasonal influenza vaccine for the first time can begin as soon as vaccine is available; these children need to receive 2 doses before the onset of influenza activity. Another group of children who should receive influenza vaccine as soon as it is available are children 6 months through 8 years of age who were vaccinated for the first time during the previous season and received only one dose; these children also need to receive 2 doses before the onset of influenza activity. (See Dosage and Administration: Dosage.)

CDC and other public health agencies continually assess the supply of seasonal influenza vaccine throughout the manufacturing period and will make any necessary recommendations regarding the need for prioritization and tiered use of the vaccine in different risk groups if there are vaccine shortages or delays in distribution. Although supplies of inactivated influenza vaccine are expected to be adequate for the 2009–2010 season, the US has experienced disruptions in the manufacture or distribution of influenza virus vaccine inactivated during several recent influenza seasons.

### **Prioritizing during Vaccine Shortages**

Prior to the influenza season each year, there are uncertainties regarding production of influenza vaccine, the number of doses that will become available, and the timing of distribution of the vaccine. The US has experienced disruptions in the manufacture or distribution of seasonal influenza virus vaccine inactivated during several of the recent influenza seasons. Whenever there are vaccine shortages, the ACIP and others state that providers should target vaccine that is available to those at high risk for serious complications associated with influenza and to health-care workers and household contacts of children younger than 6 months of age.

If recommendations are issued for priority vaccination against seasonal influenza, the recommendations do *not* apply to administration of influenza virus vaccine live intranasal. During periods when seasonal influenza virus vaccine inactivated is in short supply, use of seasonal influenza virus vaccine live intranasal is encouraged for eligible individuals (e.g., nonpregnant adults and children 2–49 years of age without underlying medical conditions that put them at high risk for influenza complications) to increase availability of the inactivated vaccine for individuals at high risk.

### **Adjunctive Use of Antiviral Agents**

Although annual vaccination against seasonal influenza is considered the primary means for preventing seasonal influenza and its complications, antiviral agents are an important adjunct for the control and prevention of influenza. However, antiviral agents should *not* be considered a substitute for immunization with seasonal influenza virus vaccine.

Considerations regarding the use of antiviral agents for the prevention or treatment of influenza during the 2009–2010 influenza season are complex because strains of seasonal influenza A and B with differing patterns of antiviral resistance are likely to circulate during the season. In addition, the 2009 pandemic influenza A (H1N1) virus, previously referred to as the novel 2009 influenza A (H1N1) virus or swine-origin influenza A (H1N1) virus, is expected to continue to circulate worldwide, including in the US.

As of August 2009, more than 98% of influenza viruses circulating in the US were 2009 influenza A (H1N1) virus, and these strains have been susceptible to neuraminidase inhibitors (oseltamivir and zanamivir) and resistant to adamantanes (amantadine and rimantadine). However, isolated cases of oseltamivir-resistant 2009 influenza A (H1N1) have been reported. In addition, surveillance data indicate that almost all seasonal influenza A (H1N1) strains have been resistant to oseltamivir, but generally have been susceptible to zanamivir and most (but not all) also have been susceptible to adamantanes. Seasonal influenza A (H3N2) and influenza B viruses generally have been susceptible to oseltamivir and zanamivir and resistant to adamantanes.

CDC has issued updated interim recommendations concerning the use of antiviral agents for the prevention and treatment of influenza, including seasonal influenza and 2009 influenza A (H1N1). The CDC recommendations are available at <http://www.cdc.gov/h1n1flu> and should be used to guide selection of the most appropriate antivirals for prevention and treatment of influenza and to prioritize use of such agents in patients at higher risk for influenza-related complications. Additional revisions to these recommendations are expected as the epidemiology and clinical presentation of 2009 influenza A (H1N1) are better understood and as surveillance data on circulating strains of seasonal influenza are collected for the 2009–2010 season. The WHO also has issued guidelines for the use of antiviral agents for the treatment and prevention of seasonal influenza or 2009 pandemic influenza A (H1N1). The WHO recommendations are available at <http://www.who.int>.

Short-term prophylaxis with antiviral agents may be indicated as an adjunct to influenza virus vaccine inactivated for high-risk individuals, household contacts of high-risk individuals, and health-care personnel who receive influenza virus vaccine after influenza activity begins since such prophylaxis may provide coverage until an immune response to the vaccine develops. In addition, antiviral prophylaxis should be considered for high-risk patients when influenza virus vaccine is contraindicated, unavailable (e.g., when there is a vaccine shortage), or expected to have low effectiveness (e.g., in patients with severe immunodeficiency or when circulating influenza strains are not antigenically similar to strains covered by available influenza vaccines). Antiviral prophylaxis also may be used in conjunction with influenza virus vaccine inactivated or alone when there is an extensive outbreak of influenza in a community, region, or institution (e.g., hospital, nursing home or other long-term care facility).

If influenza virus vaccine inactivated is administered to high-risk individuals or to their care providers (e.g., health-care personnel) after a local influenza outbreak has begun and short-term antiviral prophylaxis is indicated to provide protection until immune responses to the vaccine develop, such prophylaxis generally has been given for 2–4 weeks after vaccination in adults. Because a protective effect usually is achieved within 10–14 days after vaccination in otherwise healthy adults, the IDSA and other clinicians suggest that antiviral prophylaxis in adults can be discontinued 2 weeks after vaccination. However, children younger than 9 years of age in this situation who are receiving influenza virus vaccine inactivated for the first time may require a minimum

of 6 weeks of prophylaxis (i.e., prophylaxis for at least 4 weeks after the first vaccine dose and an additional 2 weeks after the second vaccine dose).

For further information on adjunctive prophylaxis of influenza or postexposure prophylaxis with antiviral agents, see Uses: Prevention of Influenza A Virus Infections, in Amantadine Hydrochloride 8:18.04 and see Uses: Prevention of Influenza A and B Virus Infections, in Oseltamivir Phosphate 8:18.28.

### **■ Pandemic Influenza**

Influenza viruses can cause seasonal epidemics and, occasionally, global pandemics (an epidemic that affects the whole population). Prior to 2009, the 3 most recent influenza pandemics were the 1918 Spanish flu pandemic (caused 20–50 million deaths worldwide including about 500,000 deaths in the US), the 1957 Asian flu pandemic (caused 1–4 million deaths worldwide including about 70,000 deaths in the US), and the 1968 Hong Kong flu pandemic (caused 1–4 million deaths worldwide including about 34,000 deaths in the US). On June 11, 2009, the WHO declared that the first global influenza pandemic in 41 years was occurring and issued a phase 6 pandemic alert regarding 2009 influenza A (H1N1). A phase 6 pandemic is characterized by human-to-human transmission of an animal or human-animal reassortant virus and sustained community level outbreaks of the virus in 2 or more countries in a single WHO region and sustained community level outbreaks in at least one other country in a different WHO region. (See Uses: 2009 Influenza A (H1N1) Virus Infections.)

For a pandemic to occur, a novel influenza strain that can infect humans must emerge, against which all or most of the human population has no antibody; the strain must be capable of human-to-human transmission, causing widespread illness. Usually this is the result of major antigenic shifts occurring in circulating human viruses. However, the 2009 pandemic influenza A (H1N1) virus contains a unique combination of gene segments not previously reported among human or swine influenza A in the US or elsewhere and appears to be a triple-reassortant swine influenza virus containing genes from human, swine, and avian influenza A viruses. In addition, the spread of the highly pathogenic H5N1 strain of avian influenza A in poultry in Asian and other countries that has been occurring since 2003 may represent a future pandemic threat. If the avian influenza virus reassorts with a human influenza virus (e.g., H3N2) in a dually infected individual or nonhuman mammal or if virus mutations that foster transmission occur, the resulting new virus variant could be capable of sustained human-to-human transmission. WHO states that the risk of a pandemic related to avian influenza A (H5N1) is great, but unpredictable in terms of timing and severity; all conditions for the start of a pandemic are in place except a change in the H5N1 virus that would make the virus contagious among humans.

The US Department of Health and Human Services (HHS) has issued guidance for pandemic influenza preparation and response and information on this plan is available at <http://www.hhs.gov/pandemicflu/plan/>. In addition, HHS provides updated information on influenza pandemics at <http://pandemicflu.gov>. Information on the FDA pandemic influenza preparedness strategic plan is available at <http://www.fda.gov/EmergencyPreparedness/Flu/ucm165686.htm>. The WHO also has issued guidelines for pandemic influenza preparedness and response and these guidelines are available at <http://www.who.int>.

Although vaccination is the primary strategy to reduce the impact of a pandemic, available seasonal influenza virus vaccine provides protection only against those strains from which the vaccine is prepared and closely related strains and would not provide protection against new influenza subtypes, including avian influenza strains. Therefore, US and global influenza surveillance is necessary to provide warning signals regarding emerging new strains and allow time to manufacture an appropriate vaccine.

Influenza antiviral agents may be important for prophylaxis or treatment if an influenza pandemic occurs. Because supplies of vaccine active against the pandemic strain are likely to be limited or nonexistent at the beginning of an influenza pandemic, antiviral agents may be the only virus-specific intervention available during the initial phase. During a pandemic, use of antiviral agents could reduce influenza-related morbidity, complications, hospitalizations, and other health-care needs, and might reduce mortality. Antiviral prophylaxis may have particular benefits in high risk individuals and high risk settings. (For information on use of antivirals in an influenza pandemic, see Uses: Pandemic Influenza, in Oseltamivir 8:18.28.)

### **■ 2009 Influenza A (H1N1) Virus Infections**

Seasonal influenza vaccines for the 2009–2010 influenza season are *not* expected to provide protection against infection with the 2009 pandemic influenza A (H1N1) virus, previously referred to as the novel 2009 influenza A (H1N1) virus or swine-origin influenza A (H1N1) virus. However, influenza A (H1N1) 2009 monovalent vaccine may be indicated in certain groups at highest risk for infection or influenza-related complications to prevent infection caused by this strain.

Influenza outbreaks caused by the 2009 influenza A (H1N1) virus were initially reported in several countries, including the US, beginning in March and April 2009. On June 11, 2009, the WHO declared that the first global influenza pandemic in 41 years was occurring and issued a phase 6 pandemic alert regarding 2009 influenza A (H1N1). (See Uses: Pandemic Influenza.)

The 2009 influenza A (H1N1) virus appears to be a triple-reassortant swine influenza virus containing genes from human, swine, and avian influenza A viruses. The virus contains a unique combination of gene segments not previously reported among human or swine influenza A in the US or elsewhere. However, the virus may be antigenically similar to classical swine influenza A (H1N1) viruses and triple reassortant swine influenza A (H1N1) viruses that circulate in pigs and have been associated with sporadic human infections. The 2009 influenza A (H1N1) virus is antigenically and

genetically distinct from other circulating human influenza A (H1N1), and preliminary studies indicate that a majority of the population may be susceptible to the virus.

### ■ Avian Influenza A Virus Infections

Seasonal influenza vaccines for the 2009–2010 influenza season are *not* expected to provide protection against infection with avian influenza A viruses, including avian influenza A (H5N1). Although an inactivated influenza A (H5N1) monovalent vaccine has been approved by the FDA, the vaccine is not available commercially but has been purchased by the US Federal Government for inclusion in the National Stockpile.

Avian influenza A virus refers to influenza A subtypes that occur mainly in birds but also have rarely caused infection in humans (H5N1, H7N2, H7N3, H7N7, H9N2). Avian influenza A viruses are classified as low pathogenic or high pathogenic based on genetic sequence and severity of illness in infected birds. Most avian influenza virus strains are low pathogenic and cause essentially no clinical signs in infected birds; however, these strains can mutate under field conditions to high pathogenic strains.

There have been sporadic severe and fatal human cases of infection with highly pathogenic avian influenza A (H5N1) in Asia, Africa, Europe, and the Middle East, primarily among individuals in direct or close unprotected contact with infected or dead birds. In addition, confirmed human cases of H7N2, H7N3, H7N7, and H9N2 avian influenza A infection and illness have been reported in some countries (including a few cases in Canada, the US, and the United Kingdom).

CDC recommends that health-care workers involved in the care of patients with suspected or documented avian influenza be vaccinated with the current influenza virus vaccine used to prevent seasonal influenza. In addition, CDC, the World Health Organization (WHO), and the Canadian NACI recommend vaccination with the current seasonal influenza virus vaccine for individuals involved in poultry culling operations who have direct contact with poultry potentially infected with avian influenza. Influenza vaccines used for prevention of seasonal influenza are not expected to provide protection against avian influenza A viruses, including avian influenza A (H5N1), but might reduce the risk of coinfection and thereby reduce the potential for human-avian reassortment of genes in an individual simultaneously infected with a human and avian strain. If reassortment occurs, the likelihood that an avian influenza A virus (e.g., H5N1) could be readily transmitted from person to person increases.

In response to the outbreaks of avian influenza virus in poultry and reported human cases of avian influenza A (H5N1), CDC first issued interim recommendations for evaluation, reporting, laboratory testing, and enhanced influenza surveillance for suspected avian influenza A infections in 2004. These interim recommendations have been expanded and updated and the most current recommendations regarding avian influenza A (H5N1), including recommendations for antiviral prophylaxis or treatment, are available from the CDC at <http://www.cdc.gov/flu/avian>.

### Avian Influenza Type A (H5N1)

Since 2003, there has been an ongoing zoonotic outbreak of highly pathogenic avian influenza A (H5N1) virus infection in poultry and wild birds in Asia, Africa, Europe, and the Middle East. There also have been sporadic severe and fatal human cases of infection with highly pathogenic avian influenza A (H5N1) in these countries, primarily among individuals in direct or close unprotected contact with infected or dead birds. Only limited, nonsustained, human-to-human transmission of this highly pathogenic virus appears to have occurred. The overall fatality rate in humans infected with avian influenza A (H5N1) has been high (more than 60%). The virus has not been reported to date in wild or domestic birds or in humans in the US.

Between 2003 and August 2009, 440 confirmed human cases and 262 deaths attributed to avian influenza A (H5N1) were reported to WHO. Many of these infections occurred in children and young adults (5–24 years of age) and were associated with severe respiratory illness requiring hospitalization and were frequently fatal (case-fatality proportion 68%). These outbreaks usually were associated with widespread outbreaks of highly pathogenic H5N1 influenza in domestic poultry.

The small number of human infections reported to date relative to the large number of infected birds suggests that the H5N1 avian influenza virus strain does not easily infect humans.

### Avian Influenza Type A (H7N7, H7N3, H7N2)

Outbreaks of avian influenza A (H7N7) were first reported in poultry in several farms in the Netherlands and then were reported among pigs and humans in the Netherlands and among birds in Belgium and Germany. There was a large outbreak of avian influenza A (H7N7) in commercial poultry farms in the Netherlands in 2003 that resulted in large numbers of human cases among poultry workers and their families. During this outbreak, there were at least 85 confirmed human cases and, although most patients had conjunctivitis or influenza-like illness, there was at least one death in a 57-year old veterinarian that was attributed to acute respiratory distress syndrome and complications related to influenza A (H7N7). Most cases appeared to result from direct contact with infected poultry, but there was evidence that person-to-person transmission of influenza A (H7N7) occurred among household contacts during this outbreak.

During March 2004, 2 cases of avian influenza A (H7N3) were reported in workers involved in culling poultry during an outbreak of highly pathogenic H7N3 on farms in British Columbia, Canada. One patient had unilateral conjunctivitis and nasal discharge; the other patient had unilateral conjunctivitis and headache; both illnesses resolved without hospitalization.

Human cases of avian influenza A (H7N2) have been reported rarely in the US. One case of avian influenza A (H7N2) was reported in New York in 2003 in an adult hospitalized for upper and lower tract respiratory illness; the source of the infection is

unknown. During 2002, one case of avian influenza A (H7N2) was reported in Virginia in an individual involved in culling turkeys and chickens infected with influenza A (H7N2).

During May 2007, 4 cases of avian influenza A (H7N2) were reported in workers exposed to infected poultry in Wales.

### Avian Influenza Type A (H9N2)

A few human cases of avian influenza A (H9N2) have been reported in Hong Kong and China since 1998. One case of avian influenza A (H9N2) was reported in a 5-year old child in Hong Kong in late 2003. The child had fever, cough, and nasal discharge and was hospitalized for 2 days; the source of the infection is unknown. In March 2007, China confirmed an avian influenza A (H9N2) infection in a 9-month-old girl with mild signs of disease.

### Travelers to Areas with Avian Influenza A

The CDC does *not* recommend that the general public avoid travel to any of the countries that have had poultry outbreaks or human cases of avian influenza A (H5N1). However, CDC and WHO state that travelers to these areas can reduce their risk of infection by avoiding direct contact with poultry. Specifically, the CDC recommends that such travelers avoid direct contact with all poultry (including well-appearing, sick, or dead poultry), avoid places such as poultry farms and bird markets where live poultry are raised or kept, avoid handling surfaces that may have been contaminated with poultry feces or secretions, and avoid contact with animals in live food markets. Transmission of avian influenza A (H5N1) virus to 2 persons occurred in Vietnam in 2005 through consumption of uncooked duck blood. Therefore, uncooked poultry or poultry products (including eggs and poultry blood) should not be consumed. Because influenza viruses are destroyed by heat, all foods from poultry that comes from these areas (including eggs and poultry blood) should be thoroughly cooked. Additional information for travelers to countries with known outbreaks of avian influenza A (H5N1) is available from CDC at <http://www.cdc.gov/travel>.

For additional information on avian influenza A, including recommendations for treatment and prophylaxis, see Uses: Avian Influenza A Virus Infection in Oseltamivir 8:18.28.

## Dosage and Administration

### ■ Administration

Inactivated influenza virus vaccines are administered by IM injection. The vaccines should *not* be administered IV or subcutaneously. Influenza virus vaccine also is administered intranasally to adults and children as a live, attenuated (cold-adapted) vaccine. (See Influenza Virus Vaccine Live Intranasal 80:12.)

To ensure delivery into muscle, IM injections should be made at a 90° angle to the skin using a needle length appropriate for the individual's age and body mass. In adults and adolescents, IM injection of influenza virus vaccine inactivated should preferably be made in the region of the deltoid muscle. In children 3 years of age or older, IM injections should be made into the deltoid muscle if muscle mass is adequate; alternatively, the anterolateral thigh can be used. In children 6 months to 2 years of age, IM injections should preferably be made in the anterolateral aspect of the thigh.

Vaccines should *not* be administered into the buttock muscle because of the potential for injection-associated injury to the sciatic nerve nor into any area where there may be a major nerve trunk.

Influenza virus vaccine inactivated should be inspected visually for particulate matter and discoloration prior to administration. Vials containing the vaccine should be shaken well before withdrawing a dose. Prefilled syringes should be shaken well before administering a dose. Although some manufacturers and some experts recommend that aspiration be performed after the needle has been inserted to ensure that a blood vessel has not been entered, the US Public Health Service Advisory Committee on Immunization Practices (ACIP) states that no data exist to document the necessity for this procedure.

Influenza virus vaccine inactivated should *not* be mixed with any other vaccine or solution.

Influenza virus vaccine inactivated may be administered simultaneously with other vaccines during the same health-care visit. (See Drug Interactions: Vaccines.) When multiple vaccines are administered during a single health-care visit, each vaccine should be given with a different syringe and at different injection sites. Injection sites should be separated by at least 1 inch (if anatomically feasible) to allow appropriate attribution of any local adverse effects that may occur.

Seasonal influenza virus vaccine inactivated should be administered every year before exposure to seasonal influenza. Optimum time for annual vaccination against seasonal influenza cannot be determined since influenza seasons vary in timing and duration and more than one outbreak might occur in a single community in a single year. In the US, localized influenza outbreaks indicating the start of the annual influenza season can occur as early as October; peak influenza activity often occurs in January or February, but has occurred as late as April or May. Vaccination efforts should be started each year as soon as the seasonal influenza vaccine is available (usually available beginning in September or October) and should be continued throughout influenza season.

When planning influenza vaccination efforts for the 2009–2010 influenza season, it should be considered that vaccination against the 2009 pandemic influenza A (H1N1) virus, previously referred to as the novel 2009 influenza A (H1N1) virus or swine-origin influenza A (H1N1) virus, may be indicated in addition to vaccination against seasonal

influenza in certain individuals and may create additional burden on vaccination programs and health-care providers. To reduce potential overlap between vaccination against seasonal influenza and vaccination against the 2009 pandemic influenza A (H1N1) virus, ACIP recommends that immunization against seasonal influenza be initiated as soon as the seasonal vaccine is available (e.g., September).

### ■ Dosage

Dose and dosing schedule of influenza virus vaccine inactivated for prevention of seasonal influenza depend on the individual's age, vaccination status, and specific product administered.

A single-dose regimen is used in adults and children 9 years of age or older. To promote an adequate antibody response, a 2-dose regimen is used in children 6 months to 8 years of age who have not previously received seasonal influenza vaccine or received seasonal influenza vaccine for the first time during the previous season and did not receive a second dose during the same season.

Afluria<sup>®</sup>, Fluarix<sup>®</sup>, and FluLaval<sup>®</sup> influenza virus vaccine inactivated 2009–2010 are used *only* in adults 18 years of age or older.

Fluzone<sup>®</sup> influenza virus vaccine inactivated 2009–2010 may be used in adults, adolescents, and children 6 months of age or older. Fluvirin<sup>®</sup> influenza virus vaccine inactivated 2009–2010 may be used in adults, adolescents, and children 4 years of age or older.

### Adult Dosage

**Afluria<sup>®</sup>, Fluarix<sup>®</sup>, FluLaval<sup>®</sup>, Fluvirin<sup>®</sup>, or Fluzone<sup>®</sup>.**

The usual adult dosage for prevention of seasonal influenza infection is 0.5 mL administered IM as a single dose.

### Pediatric Dosage<sup>®</sup>

**Fluzone<sup>®</sup>.**

In adolescents and children 9 years of age or older, the usual dosage of Fluzone<sup>®</sup> for prevention of seasonal influenza infection is 0.5 mL administered IM as a single dose.

Children 3–8 years of age who have not previously received seasonal influenza vaccine or received seasonal influenza vaccine for the first time during the previous season and did not receive a second dose during the same season should receive two 0.5-mL doses of Fluzone<sup>®</sup> administered IM at least 1 month apart.

Children 3–8 years of age who received 2 doses of seasonal influenza vaccine during the previous season or at least 1 dose of seasonal influenza vaccine 2 or more years ago should receive a single 0.5-mL IM dose of Fluzone<sup>®</sup>.

Children 6–35 months of age who have not previously received seasonal influenza vaccine or received seasonal influenza vaccine for the first time during the previous season and did not receive a second dose during the same season should receive two 0.25-mL doses of Fluzone<sup>®</sup> administered IM at least 1 month apart.

Children 6–35 months of age who received 2 doses of seasonal influenza vaccine during the previous season or at least 1 dose of seasonal influenza vaccine 2 or more years ago should receive a single 0.25-mL IM dose of Fluzone<sup>®</sup>.

**Fluvirin<sup>®</sup>.**

In adolescents and children 9 years of age or older, the usual dosage of Fluvirin<sup>®</sup> for prevention of seasonal influenza infection is 0.5 mL administered IM as a single dose.

Children 4–8 years of age who have not previously received seasonal influenza vaccine or received seasonal influenza vaccine for the first time during the previous season and did not receive a second dose during the same season should receive two 0.5-mL doses of Fluvirin<sup>®</sup> administered IM at least 1 month apart.

Children 4–8 years of age who received 2 doses of seasonal influenza vaccine during the previous season or 1 dose of seasonal influenza vaccine 2 years ago should receive a single 0.5-mL IM dose of Fluvirin<sup>®</sup>.

## Cautions

### ■ Local Effects

The most frequent adverse effects of seasonal influenza virus vaccine inactivated are local effects. Soreness at the injection site has been observed in 10–64% of individuals receiving seasonal influenza virus vaccine inactivated. These local reactions generally are mild to moderate in severity and persist up to 2 days, but rarely interfere with normal activities. Acetaminophen (e.g., 650 mg in adults at the time of vaccination and every 4 hours for 3 additional doses) may reduce the incidence of local reactions (e.g., soreness).

There is some evidence that adverse local effects (e.g., soreness) of seasonal influenza virus vaccine inactivated may be reported more frequently in children and in women. In a study of asthmatic children 9 months to 18 years of age, local pain and swelling were reported in 20–28% of vaccinees; in a study in children 6 months to 4 years of age with chronic heart or lung disease, 23% had local reactions to the vaccine. Results of another study in children indicate that there is no difference in the incidence of local reactions to influenza vaccination between those with high-risk medical conditions and healthy children.

The frequency and severity of local reactions (e.g., tenderness, erythema) may be increased following administration of the vaccines using a multidose jet injector compared with a conventional syringe and needle.

### ■ Systemic Effects

Because inactivated influenza virus vaccines contain only inactivated influenza viruses, they cannot cause influenza infection. Cases of respiratory illness that occur following administration of seasonal influenza virus vaccine inactivated are coincidental and unrelated to influenza vaccination. Unfortunately, because the timing of seasonal influenza immunization programs coincides with peak periods for other respiratory illnesses, many patients conclude incorrectly that the development of a respiratory illness following vaccination resulted from the vaccine itself, and then often avoid future influenza vaccination. Confusion between lay and medical use of the term “flu” also may contribute to patient misconceptions. Therefore, patients should be advised that the vaccine contains noninfectious killed viruses and cannot cause influenza (the “flu”); they also should be advised of the coincidental and unrelated nature of any temporally associated respiratory illness.

The major adverse effects of seasonal inactivated influenza vaccines are systemic reactions, including fever, malaise, myalgia, and other systemic manifestations, which generally begin 6–12 hours after administration of the vaccine and persist for 1 or 2 days. Such systemic reactions occur infrequently and usually are attributed to the inactivated influenza virus contained in the vaccine and occur most frequently in young children and other individuals who have not been exposed previously to the influenza virus antigens contained in the vaccine. In a study of healthy children receiving seasonal influenza virus vaccine inactivated, fever was reported in 11.5, 4.6, and 5.1% of those aged 1–5, 6–10, and 11–15 years, respectively. In another study in children 6 months to 4 years of age, fever occurred in 27% and irritability and insomnia occurred in 25%. Results of placebo-controlled studies in healthy young adults and geriatric individuals indicate that the incidence of adverse systemic effects (e.g., fever, malaise, myalgia, headache) following administration of split-virus seasonal inactivated influenza vaccine is similar to that reported following placebo injections.

Headache, GI manifestations (e.g., nausea), and lymphadenitis also have been reported following administration of seasonal inactivated influenza vaccines. Vasculitis and vasodilation/flushing have been reported in postmarketing surveillance. Rarely, administration of seasonal influenza virus vaccine inactivated has been associated temporally with the development of angiopathy, microscopic polyangiitis (vasculitis), uveitis, dermatomyositis, or arthritis or other rheumatic complications. It is unclear whether patients with rheumatoid arthritis are at increased risk of arthritis flare following influenza vaccination. At least one case of acute symmetrical polyarthropathy, orbital myositis, and posterior scleritis was postulated as being a sensitivity reaction to the vaccine. Although a causal relationship has not been established, the onset of Gianotti-Crosti syndrome (a papular acrodermatitis) in a hepatitis B virus-infected woman and of erythromelalgia (palmar and plantar erythema, burning pain, and increased skin temperature) in a child were associated temporally with administration of seasonal inactivated influenza virus vaccine.

### Oculorespiratory Syndrome

During the 2000–2001 influenza vaccination season, an oculorespiratory syndrome (ORS) was reported in at least 960 individuals who received seasonal influenza virus vaccine inactivated in Canada. The syndrome was defined as the presence of bilateral red eyes and/or at least one of several respiratory symptoms (i.e., cough, wheeze, chest tightness, difficulty breathing, difficulty swallowing, hoarseness, sore throat) and/or facial edema occurring within 24 hours after influenza vaccination and resolving within 48 hours. The syndrome generally was mild and self-limited. Although the pathophysiologic mechanism for ORS is unknown, it was considered distinct from IgE-mediated allergy. Most reported cases (96%) occurred following receipt of one specific seasonal influenza virus vaccine inactivated preparation (Fluviral<sup>®</sup> S/F; not commercially available in the US). To further evaluate the risk of ORS, controlled studies were done in Canada the following year using the 2001–2002 Fluviral<sup>®</sup> S/F preparation in adults with or without a history of ORS following influenza vaccination the previous year. Results in adults without a prior history of the adverse effect indicated that the risk of developing ORS, defined as onset of bilateral red eyes, respiratory symptoms (cough, wheeze, chest tightness, difficulty breathing, difficulty swallowing, hoarseness or sore throat), and/or facial swelling within 2–24 hours after vaccination, was 6.3% in those who received Fluviral<sup>®</sup> S/F and 3.5% in those who received placebo. However, the study in those with a prior history of ORS was terminated early because the vaccine-attributable risk of the syndrome exceeded 10% in these individuals.

Approximately 5–34% of patients who previously experienced ORS have a recurrence attributable to seasonal influenza vaccine, but most recurrences are less severe than the previous episode. Individuals who have a recurrence of ORS following subsequent vaccination do not necessarily experience further episodes with future vaccinations.

### Sensitivity Reactions

Immediate, presumably allergic reactions to seasonal influenza virus vaccine inactivated, including urticaria, angioedema, anaphylaxis, and allergic asthma, occur rarely. These hypersensitivity reactions may result from sensitivity to some vaccine component; the majority of such reactions most likely are related to residual egg protein that may be present in minute amounts. (See Sensitivity Reactions under Cautions: Precautions and Contraindications.) Hensch-Schoenlein purpura, which appeared to be a hypersensitivity reaction, has been reported in at least one individual who received influenza virus vaccine inactivated.

Although bronchoprovocation tests have shown increased bronchial reactivity in some asthmatics for several days after vaccination with seasonal influenza virus vaccine inactivated and an association between vaccination and asthma exacerbations

and/or decreased pulmonary function (e.g., peak expiratory flow) has been reported occasionally, such studies were poorly designed (e.g., no placebo control) and other studies have been unable to confirm such findings. One randomized, double-blind, placebo-controlled cross-over study in children and adults 3–64 years of age with asthma found no increase in asthma exacerbations during the 2 weeks after administration of influenza virus vaccine inactivated. Therefore, most experts, including the US Public Health Service Advisory Committee on Immunization Practices (ACIP), the American Academy of Pediatrics (AAP), and the Canadian National Advisory Committee on Immunization (NACI), recommend annual vaccination with seasonal influenza virus vaccine inactivated in asthmatics since the benefits of influenza vaccination outweigh the risks of asthma exacerbations and influenza infection.

### **Guillain-Barré Syndrome**

In 1976, a temporal association was noted between administration of A/New Jersey/76 (swine) influenza vaccine and Guillain-Barré syndrome (GBS, polyradiculoneuritis). Epidemiologic evidence indicates that the associated risk between administration of this vaccine and GBS did not extend beyond 6 weeks after vaccination. GBS is characterized by ascending symmetric paralysis that usually begins in the legs and usually is self-limited and reversible. Although the immunologic events leading to GBS have not been fully elucidated, the syndrome is mediated through an immune response that results in direct destruction of either the myelin sheath surrounding the peripheral nerves or the axon itself, and it may or may not follow triggering events such as vaccination. The rate of GBS that exceeded the background rate of 10–20 cases per million in adults who received A/New Jersey/76 (swine) influenza vaccine was slightly less than 10 additional cases per million vaccinees.

An increased risk of developing GBS was not clearly evident with subsequent influenza vaccine formulations prepared from other virus strains, but it is difficult to estimate precisely the risk for a condition as rare as GBS. In addition, vaccinees who received the A/New Jersey/76 (swine) influenza vaccine have not been shown to exhibit an increased risk of GBS with subsequent vaccine formulations.

During 3 of 4 influenza seasons studied from 1977–1991, point estimates of overall relative risks of GBS among recipients of seasonal inactivated influenza vaccine were elevated slightly; however, in none of these studies was the overall elevation statistically significant. In the 1992–1993 and 1993–1994 seasons, an increase to 1.7 of the overall relative risk of GBS adjusted for age, gender, and vaccine season was observed during the 6 weeks after vaccination, with the combined number of GBS cases peaking 2 weeks after vaccination. Although there was concern that the increased number of case reports of GBS associated with the 1993–1994 season relative to the 1992–1994 season may have represented an increased GBS risk with the 1993–1994 vaccine, epidemiologic analysis showed that there was no increase in vaccine-associated GBS between these seasons. Estimates from these seasons suggest slightly more than one additional case of GBS per million influenza vaccinees.

Investigations to date suggest no large increase in GBS associated with influenza vaccine (other than the swine influenza vaccine in 1976) and if influenza vaccine does pose a risk it probably is quite small (i.e., slightly more than 1 case per million vaccinees). Cases of GBS following influenza infection have been reported, but no epidemiologic studies have documented an association. Good evidence exists that several infectious illnesses, most notably *Campylobacter jejuni* as well as upper respiratory infections in general, are associated with GBS.

Even if GBS truly were an adverse effect of influenza virus vaccine inactivated in the years subsequent to 1976, the estimated risk for GBS of approximately 1 additional case per million vaccinees is much less than the 1976 rate and substantially less than the risk for severe influenza, which can be prevented by vaccination in all age groups, particularly for those 65 years of age and older and for individuals who have medical indications for vaccination. There is no evidence that the case-fatality ratio for GBS differs among vaccinated and unvaccinated individuals.

During influenza epidemics from 1979–2001, the estimated annual average of influenza-associated hospitalizations was 226,000. Approximately 36,000 deaths per season occurred during 1990–1999; geriatric adults account for more than 90% of deaths attributed to pneumonia and influenza. Therefore, the ACIP states that the potential benefits of influenza vaccination in preventing serious illness, hospitalization, and death greatly outweigh the possible risks for vaccine-associated GBS.

The risk of developing GBS is increased substantially in individuals with a history of GBS. Therefore, the likelihood of *coincidentally* developing GBS after influenza vaccination probably is greater among those with a history of GBS than among those without such a history. Whether a causal relationship exists between vaccination and this risk of recurrence of GBS is not known. (See Cautions: Precautions and Contraindications.)

The AAP states that influenza vaccines should not be used in children who developed GBS within 6 weeks after a dose of any influenza vaccine. The ACIP states that the benefits of seasonal influenza vaccination may outweigh risks in individuals with a history of GBS who are at high risk for severe influenza-related complications. However, it may be prudent to avoid influenza vaccine in individuals who are not at high risk for severe influenza complications if they experienced GBS within 6 weeks after previous influenza vaccination.

### **Other Neurologic Effects**

Neurologic disorders (not defined as GBS) have been temporally associated with seasonal influenza vaccination, including encephalopathy, encephalomyelitis, amyotrophic lateral sclerosis (Charcot syndrome, Lou Gehrig disease), trigeminal neuralgia, optic neuritis/neuropathy, partial facial paralysis, brachial neuritis,

nonspecific neuritis, demyelinating disorder, labyrinthitis, meningitis, paresthesia, hypoesthesia, and brachial plexus neuropathy. Transverse myelitis has been reported rarely.

A placebo-controlled study of seasonal influenza immunization in patients with multiple sclerosis found no association between the rate of neurologic exacerbation of the disease postvaccination nor a change in disease progression over the subsequent 6 months of follow-up. In another study that surveyed patients with multiple sclerosis who were identified through a registry of the disease, no deleterious effect from vaccination was observed in patients with primary progressive multiple sclerosis, and the neurologic exacerbation rate was substantially greater following influenza illness than following vaccination in patients with relapsing multiple sclerosis.

Seasonal influenza virus vaccine inactivated is *not* known to predispose to the development of Reye's syndrome.

## **■ Precautions and Contraindications**

### **Sensitivity Reactions**

While the potential exists for hypersensitivity reactions to any vaccine component, immediate hypersensitivity reactions to seasonal inactivated influenza virus vaccines are rare and most likely related to residual egg protein present in the vaccine.

Seasonal inactivated influenza virus vaccines should *not* be administered to individuals with a history of immediate hypersensitivity reaction, especially anaphylactic reactions, to a previous dose, to chicken eggs or egg products, or to other ingredients in the respective vaccine formulation without first consulting a clinician and conducting an appropriate allergy evaluation and possible desensitization.

Although available seasonal influenza virus vaccines contain only small quantities of egg protein, this protein may induce immediate hypersensitivity reactions in individuals with severe egg allergy. Individuals who have developed urticaria, had swelling of the lips or tongue, or experienced acute respiratory distress or circulatory collapse following ingestion of eggs should consult a clinician for appropriate evaluation to assist in determining whether seasonal influenza vaccination can be undertaken safely or should be deferred. Individuals who have had a documented IgE-mediated hypersensitivity reaction to eggs and individuals who because of occupational exposure to egg protein have developed signs of occupational asthma or other allergic response from exposure to egg protein also may be at increased risk for hypersensitivity reactions following administration of seasonal influenza virus vaccine inactivated, and similar consultation with a clinician should be considered. Asking individuals whether they can eat eggs without adverse effects is a reasonable method to screen for those who may be at risk from receiving seasonal influenza virus vaccine inactivated. Individuals who are able to eat eggs or egg products safely usually can receive seasonal influenza virus vaccine inactivated; those with a history of anaphylactic or other immediate hypersensitivity reaction (e.g., hives, angioedema, allergic asthma) to eggs or egg proteins should *not* receive the vaccine. The AAP states that, although seasonal influenza virus vaccine inactivated has been administered safely to such children after skin testing and desensitization, children with severe anaphylactic reactions to eggs generally should *not* receive influenza vaccine because of their risk of reactions, the likely need for annual vaccination, and the availability of antiviral agents for prophylaxis against influenza infection.

Because Afluria<sup>®</sup> contains trace amounts of neomycin sulfate (0.2 picograms or less per dose) and polymyxin B (0.03 picograms or less per dose), the manufacturer states that the vaccine is contraindicated in individuals hypersensitive to these anti-infectives.

Fluvirin<sup>®</sup> also contains neomycin (2.5 mcg or less) and polymyxin B (3.75 mcg or less). Neomycin allergy usually results in delayed-type (cell-mediated) hypersensitivity reactions manifested as contact dermatitis. The ACIP and AAP state that vaccines containing trace amounts of neomycin should not be used in individuals with a history of anaphylactic reactions to neomycin, but may be considered in those with a history of delayed-type neomycin hypersensitivity if the benefits of vaccination outweigh risks.

All multiple-dose vials of seasonal influenza virus vaccine contain thimerosal as a preservative; some preparations of the vaccine in prefilled syringes are preservative-free but contain trace amounts of thimerosal from the manufacturing process. (See Thimerosal Precautions under Cautions: Precautions and Contraindications.) Hypersensitivity reactions to thimerosal have been reported in some individuals. These reactions usually manifest as local, delayed-type hypersensitivity reactions (e.g., erythema, swelling), but a generalized reaction manifested as pruritus and an erythematous, maculopapular rash on all 4 extremities has been reported rarely. Even when patch or intradermal tests for thimerosal sensitivity are positive, most individuals do not develop hypersensitivity reactions to thimerosal administered as a component of vaccines. ACIP states that a history of delayed-type hypersensitivity to thimerosal is not a contraindication to use of vaccines that contain thimerosal.

Some components of the commercially available prefilled syringes containing Fluarix<sup>®</sup> inactivated influenza virus vaccine (tip cap, plunger) contain natural latex proteins in the form of dry natural rubber and/or natural rubber latex (see the manufacturer's labeling). Some individuals may be hypersensitive to natural latex proteins found in a wide range of medical devices, including such packaging components, and the level of sensitivity may vary depending on the form of natural rubber present; rarely, hypersensitivity reactions to natural latex proteins have been fatal. Therefore, while the specific risk cannot necessarily be predicted, health-care professionals should take appropriate precautions when administration of such influenza virus vaccine preparations is considered for individuals with a history of natural latex

sensitivity. The ACIP and others state that a history of nonsevere allergy to latex is not a contraindication to influenza virus vaccine inactivated.

### ***Guillain-Barré Syndrome (GBS) and Other Neurologic Conditions***

The AAP states that influenza vaccine should not be used in children who developed GBS within 6 weeks after a dose of any influenza vaccine. The ACIP states that, although it may seem prudent to avoid influenza vaccination in individuals who developed GBS within 6 weeks of a previous influenza vaccination, the established benefits of influenza vaccination in preventing serious illness, hospitalization, and death justify annual immunization for most individuals with a history of GBS who are at high risk for severe influenza-related complications. However, as an alternative, the ACIP states that clinicians might consider the use of antiviral prophylaxis for these individuals. (See Guillain-Barré Syndrome under Cautions: Systemic Effects.)

Based principally on the theoretical concerns, some clinicians recommend that influenza vaccination probably should be avoided in patients with chronic inflammatory demyelinating polyneuropathy, except in those at substantial risk from influenza complications.

### ***Individuals with Altered Immunocompetence***

Seasonal inactivated influenza virus vaccine may be administered to individuals immunosuppressed as the result of disease or immunosuppressive therapy. However, the possibility that the immune response to the vaccine and efficacy may be reduced in these individuals should be considered.

The Centers for Disease Control and Prevention (CDC), National Institutes of Health (NIH), Infectious Diseases Society of America (IDSA), AAP, and other experts state that HIV-infected children, adolescents, and adults should receive annual vaccination against seasonal influenza; however the parenteral inactivated influenza vaccine (not the intranasal live vaccine) should be used for prevention of seasonal influenza in HIV-infected individuals. Data are limited regarding the safety of seasonal parenteral influenza virus vaccine inactivated in HIV-infected individuals, but there is no evidence that use of the vaccine has any clinically important effect on HIV infection or immunocompetence. However, antibody response may be reduced in HIV-infected individuals and is inversely correlated with the severity of the disease. The vaccine has been highly effective in preventing symptomatic, laboratory-confirmed influenza infection in HIV-infected individuals with mean CD4<sup>+</sup> T-cell counts of 400/mm<sup>3</sup>, but may be less effective in those with more advanced disease and lower CD4<sup>+</sup> T-cell counts (e.g., less than 100/mm<sup>3</sup>). A second dose of influenza vaccine does not appear to improve immune response in these individuals; use of influenza antiviral prophylaxis can be considered.

Influenza vaccination may not be effective if given less than 6 months after hematopoietic stem cell transplantation (HSCT).

### ***Thimerosal Precautions***

Although there is no convincing evidence that the low concentrations of thimerosal (a mercury-containing preservative) contained in some vaccines is harmful to vaccine recipients, efforts to eliminate or reduce the thimerosal content in vaccines is recommended as a prudent measure to reduce mercury exposure in infants and children and part of an overall strategy to reduce mercury exposures from all sources, including food and drugs.

The toxicity of mercury is affected by many variables, including the elemental form and amount of mercury involved in the exposure, route of entry, and age during exposure. Mercury is ubiquitous in the environment and is found in water, soil, plants, and animals, usually as inorganic mercury salts. Mercury accumulates in the aquatic food chain, principally as methylmercury, and one of the most common environmental exposures to organic mercury is through consumption of predator fish. Methylmercury is less readily eliminated from the body than inorganic mercury and is a known neurotoxin.

Thimerosal is a mercury-containing organic compound (organomercurial) that is used as a preservative in vaccines and other biologicals. Thimerosal is approximately 50% mercury by weight and is metabolized or degraded into ethylmercury and thiosalicylate. Ethylmercury is a different chemical entity than methylmercury. Although the toxicologic profile of ethylmercury derived from thimerosal is believed to be similar to that of ethylmercury from other sources, there is little data regarding the comparative toxicities of ethyl- versus methylmercury.

As part of an ongoing review of biologic products in response to the Food and Drug Administration (FDA) Modernization Act of 1997, FDA conducted a comprehensive review of the use of thimerosal in childhood vaccines and evaluated the amount of mercury an infant might receive with the US recommended childhood immunization schedule. Because there were no existing guidelines for exposure to ethylmercury, FDA used existing guidelines for exposure to methylmercury that suggested that safe exposure levels for methylmercury range from 0.1 mcg/kg daily (Environmental Protection Agency [EPA]) to 0.47 mcg/kg daily (World Health Organization [WHO]). More recently, some experts have suggested that maximum methylmercury exposure levels of 0.1 mcg/kg daily are scientifically justified for protection of human health.

Using data regarding the vaccine preparations available at the time of the review (1999), the FDA determined that the maximum cumulative exposure to mercury from the multiple vaccines in the recommended childhood immunization schedule was within the acceptable limits for methylmercury exposure set by WHO, FDA, and the US Agency for Toxic Substances and Disease Registry (ATSDR); however, depending on the specific vaccine formulations and the weight of the infant, use of multiple thimerosal-containing vaccines during the first 6 months of life potentially could expose some

infants to cumulative levels of mercury that were higher than those recommended by EPA. As a result, vaccine manufacturers and FDA worked to develop and expedite approval of vaccine formulations that either had no mercury-containing preservatives (thimerosal-free) or greatly reduced concentrations of thimerosal (thimerosal-reduced).

When thimerosal is used as a preservative in vaccines, it is present in concentrations up to 0.01% (up to 50 mcg of thimerosal per 0.5 mL or up to approximately 25 mcg of mercury per 0.5 mL). According to FDA, a vaccine is thimerosal-free if no thimerosal can be measured (i.e., thimerosal content is below the limits of detection). Thimerosal-reduced vaccines do not contain thimerosal as a preservative, but may contain trace amounts (1 mcg or less of mercury per dose) from the manufacturing process. Therefore, some vaccines may be preservative-free but may have trace amounts of thimerosal remaining from the manufacturing process. FDA states that these trace amounts are not considered clinically important and would not result in mercury exposure exceeding existing federal guidelines.

As a result of efforts initiated in 1999 to remove or reduce thimerosal in vaccines and expedite development and approval of preservative-free vaccines, all vaccines included in the US Childhood and Adolescent Immunization Schedule (see Immunization Schedules, US 80:00) are currently commercially available in the US as preparations that either are thimerosal-free or contain only trace amounts of thimerosal. However, there still are antivenins and some vaccines commercially available in the US that contain thimerosal as a preservative, including some preparations of influenza virus vaccine inactivated, some preparations of tetanus toxoid adsorbed, meningococcal polysaccharide vaccine (MPSV4; Menomune<sup>®</sup>), and Japanese encephalitis virus vaccine.

Influenza virus vaccine inactivated is now commercially available in prefilled syringes as preservative-free formulations that do not contain thimerosal and in prefilled syringes as preservative-free formulations that contain only trace amounts of thimerosal from the manufacturing process (1 mcg or less of mercury per 0.5-mL dose). Only multiple-dose vials of inactivated influenza virus still contain thimerosal as a preservative (25 mcg or less of mercury per 0.5-mL dose). Influenza virus vaccine live intranasal does not contain thimerosal.

Although it was suggested that thimerosal in vaccines theoretically could have adverse effects in vaccine recipients, there is no conclusive evidence that the low levels of thimerosal contained in vaccines cause harm in vaccine recipients. A link between thimerosal in vaccines and neurodevelopmental disorders in children (autism, attention deficit/hyperactivity disorder [ADHD], speech or language delay) possibly related to mercury neurotoxicity has been theorized; however, considerable evidence has accumulated that supports the absence of substantial risk for neurodevelopmental disorders or other harm resulting from exposure to thimerosal-containing vaccines. In 2004, the Immunization Safety Review Committee of the Institute of Medicine (IOM) examined the hypothesis that thimerosal-containing vaccines are causally associated with autism and concluded that the body of epidemiologic evidence favors rejection of a causal relationship between these vaccines and autism.

Analysis of adverse effects reported to the Vaccine Adverse Event Reporting System (VAERS) indicate that there is no difference in the incidence of injection site reactions, rash, or infections in infants 6–23 months of age who received preservative-containing (thimerosal-containing) influenza virus vaccine inactivated compared with those who received preservative-free preparations of the vaccine. To date, the only adverse effects known to be caused by thimerosal contained in vaccines are hypersensitivity reactions. (See Sensitivity Reactions under Cautions: Precautions and Contraindications.) There has been no convincing evidence that toxicity has occurred as the result of thimerosal contained in vaccines, but mercury toxicity has been observed in patients who received extremely high overdosage of other thimerosal-containing products (total thimerosal doses ranging from approximately 3 mg/kg to several hundred mg/kg). There are data indicating that mercury concentrations in blood of infants 2–6 months of age who received thimerosal-containing vaccines are considerably lower than concentrations associated with toxic effects. The AAP states that infants and children who have received thimerosal-containing vaccines do not need to have blood, urine, or hair tested for mercury because the concentrations of mercury would be quite low and would not require treatment.

The US Public Health Service (USPHS), ACIP, AAP, American Academy of Family Physicians (AAFP), and other experts state that use of vaccines that contain thimerosal is preferable to withholding vaccination since failure to provide protection against vaccine-preventable diseases may represent an immediate threat, especially in infants. ACIP states that benefits of influenza vaccination for all recommended groups (including pregnant women and young children) outweigh concerns related to theoretical risks of thimerosal exposure from vaccination with preparations containing thimerosal. AAP states that the benefits of protecting children (including children at high risk with underlying CNS disorders) against the known risks of influenza outweigh the hypothetical risks associated with the minute amounts of thimerosal contained in some currently available influenza vaccine preparations.

Afluria<sup>®</sup> is commercially available in 0.5-mL prefilled syringes as a preservative-free formulation (thimerosal was not used in the manufacturing process) and in multiple-dose vials that contain thimerosal as a preservative (24.5 mcg of mercury per 0.5-mL dose).

Fluarix<sup>®</sup> is commercially available in 0.5-mL prefilled syringes as a preservative-free formulation that does not contain thimerosal.

FluLaval<sup>®</sup> is commercially available in multiple-dose vials that contain thimerosal as a preservative (25 mcg of mercury per 0.5-mL dose).

Fluvirin<sup>®</sup> is commercially available in the US in multiple-dose vials that contain thimerosal as a preservative (25 mcg of mercury per 0.5-mL dose) and in 0.5-mL prefilled syringes as a preservative-free formulation that contains only trace amounts of thimerosal from the manufacturing process (1 mcg or less of mercury per 0.5-mL dose).

Fluzone<sup>®</sup> is commercially available in 0.25- and 0.5-mL prefilled syringes and in 0.5-mL vials as a preservative-free formulation (thimerosal was not used in the manufacturing process) and also is available in multiple-dose vials as a formulation containing thimerosal as a preservative (25 mcg of mercury per 0.5-mL dose).

### **Limitations of Vaccine Effectiveness**

Seasonal inactivated influenza virus vaccine may not protect all vaccine recipients against influenza. In addition, it may require up to 2 weeks for protection to develop following seasonal influenza vaccination.

Seasonal influenza vaccine is formulated annually to contain influenza A and B antigens predicted to represent strains of influenza virus likely to circulate in the US during the upcoming influenza season. Efficacy of the seasonal vaccine during any given year depends on how closely viral strains represented in the vaccine match viral strains circulating during the season.

Influenza virus vaccine inactivated for the 2009–2010 influenza season is *not* expected to provide protection against the 2009 pandemic influenza A (H1N1) virus, previously referred to as the novel 2009 influenza A (H1N1) virus or swine-origin influenza A (H1N1) virus, and is *not* expected to provide protection against infection with avian influenza A viruses, including avian influenza A (H5N1).

### **Concomitant Illness**

The decision whether to administer or delay administration of seasonal influenza virus vaccine in an individual with a current or recent febrile illness depends largely on the severity and etiology of the illness. Immunization of individuals with acute, moderate or severe febrile illness, including febrile respiratory or other active infection, generally should be deferred until they have recovered to avoid superimposing adverse effects of the vaccine on the underlying illness or to avoid mistakenly concluding that a manifestation of the underlying illness resulted from vaccination. Acute minor illness, such as mild diarrhea, mild upper respiratory infection (with or without low-grade fever), or other low-grade febrile illness, does not preclude vaccination.

### **Individuals with Bleeding Disorders**

Because bleeding may occur following IM administration of influenza vaccine in individuals with thrombocytopenia or a bleeding disorder (e.g., hemophilia) or in those receiving anticoagulant therapy, caution should be used in such individuals.

ACIP states that vaccines may be given IM to individuals who have bleeding disorders or are receiving anticoagulant therapy if a clinician familiar with the patient's bleeding risk determines that the preparation can be administered with reasonable safety. In these cases, a fine needle (23 gauge) should be used to administer the vaccine, and firm pressure applied to the injection site (without rubbing) for at least 2 minutes. If the patient is receiving antihemophilia therapy, the IM vaccine should be administered shortly after a scheduled dose of such therapy. Vaccine recipients and/or their family members should be advised about the risk of hematoma from IM injections.

### **Improper Storage and Handling**

Improper storage or handling of vaccines may result in loss of vaccine potency and reduced immune response in vaccinees.

All vaccines should be inspected upon delivery and monitored during storage to ensure that the appropriate storage temperature is always maintained. (See Stability under Chemistry and Stability.)

Vaccine that has been mishandled or has not been stored at the recommended temperature should not be administered. If there are concerns about mishandling, the manufacturer or state or local health departments should be contacted for guidance on whether the vaccine is usable.

### **■ Pediatric Precautions**

Safety and efficacy of Fluzone<sup>®</sup> influenza virus vaccine inactivated 2009–2010 have not been established in infants younger than 6 months of age.

Safety and efficacy of Fluvirin<sup>®</sup> influenza virus vaccine inactivated 2009–2010 have not been established in children younger than 4 years of age.

Afluria<sup>®</sup>, Fluarix<sup>®</sup>, and FluLaval<sup>®</sup> influenza virus vaccine inactivated 2009–2010 should not be used in children younger than 18 years of age.

Safety and efficacy of seasonal influenza virus vaccine inactivated have not been established in infants younger than 6 months of age. Influenza virus vaccine inactivated is less immunogenic in infants younger than 6 months of age than in those 6–18 months of age. Because seasonal influenza virus vaccine inactivated is not indicated in infants younger than 6 months of age, all household and other close contacts (e.g., day-care providers) of infants younger than 6 months of age should be vaccinated against seasonal influenza using vaccine appropriate for their age and target group since this may provide some protection against seasonal influenza for these young infants.

The ACIP states that benefits of influenza vaccination for children outweigh theoretical risks from thimerosal exposure by vaccination with preparations containing thimerosal and any available age-appropriate inactivated influenza vaccine can be used in children. The AAP states that the benefits of protecting children against the known risks of influenza outweigh the hypothetical risks associated with the minute amounts of thimerosal contained in some currently available influenza vaccine preparations. (See Thimerosal Precautions under Cautions: Precautions and Contraindications.)

### **■ Geriatric Precautions**

Clinical studies and other clinical experience with seasonal influenza virus vaccine inactivated reveal no overall differences in safety between geriatric individuals and younger patients; however, the vaccine may be less immunogenic in geriatric individuals.

### **■ Mutagenicity and Carcinogenicity**

The manufacturers state that it is not known if seasonal influenza virus vaccine inactivated is mutagenic or carcinogenic.

### **■ Pregnancy, Fertility, and Lactation**

#### **Pregnancy**

Animal reproduction studies have not been performed with seasonal influenza virus vaccine inactivated.

The manufacturers state that it is not known if seasonal influenza virus vaccine inactivated can cause fetal harm when administered to pregnant women and state that the vaccine should be administered during pregnancy only when clearly needed.

Because pregnant women are at risk for influenza-related complications, ACIP and other experts recommend that all women who are pregnant or will be pregnant during the influenza season receive influenza virus vaccine inactivated for prevention of seasonal influenza infection, including those without underlying influenza risk factors.

The ACIP, American College of Obstetricians and Gynecologists (ACOG), American Academy of Family Physicians (AAFP), NIH, IDSA, and other experts state that pregnant women should receive influenza virus vaccine inactivated (not influenza virus vaccine live intranasal) for prevention of seasonal influenza. Although the ACIP previously suggested that avoiding influenza vaccine during the first trimester of pregnancy was a reasonable precaution to minimize any concern over the theoretical risk of teratogenicity, available data to date indicate that influenza virus vaccine inactivated does not cause fetal harm when administered to pregnant women. One study in approximately 2000 pregnant women who received the inactivated vaccine during pregnancy did not reveal evidence of adverse effects during infancy or early childhood. Although more data are needed to confirm the safety of vaccination during pregnancy, the parenteral influenza vaccine available in the US is an inactivated virus vaccine, and no evidence exists of risk from vaccinating pregnant women with an inactivated virus. In addition to providing potential benefit to the mother, transplacental distribution of antibodies to the fetus following maternal vaccination also may provide some protection in infants.

The ACIP states that benefits of seasonal influenza vaccination for pregnant women outweigh theoretical risks from thimerosal exposure by vaccination with preparations containing thimerosal, and no preference is indicated for use of inactivated influenza vaccine preparations that do not contain thimerosal as a preservative. (See Thimerosal Precautions under Cautions: Precautions and Contraindications.)

During 2000–2003, an estimated 2 million pregnant women were vaccinated with seasonal influenza virus vaccine inactivated, and only 20 adverse events in women who received the vaccine were reported to the Vaccine Adverse Event Reporting System (VAERS). These adverse events included 9 injection-site reactions and 8 systemic reactions (e.g., fever, headache, myalgias). In addition, 3 miscarriages were reported, but these were not known to be causally related to vaccination. Similar results have been reported in certain smaller studies, and a recent international review of data on the safety of influenza virus vaccine inactivated concluded that no evidence exists to suggest harm to the fetus.

#### **Fertility**

The manufacturers state that it is not known if seasonal inactivated influenza vaccine can affect fertility.

#### **Lactation**

It is not known whether parenteral inactivated influenza vaccine is distributed into milk. The manufacturers recommend that seasonal inactivated influenza vaccine be used with caution in women who are breastfeeding.

Although specific data are not available, the ACIP and AAFP state that breastfeeding generally is not a contraindication to administration of inactivated vaccines since inactivated organisms in these vaccines do not multiply within the body and such vaccines appear to pose no special problems for the mother or her nursing infant. There also is no evidence that breast-feeding can adversely affect the immune response to the vaccine.

### **Drug Interactions**

#### **■ Aldesleukin**

There is some evidence that aldesleukin (interleukin-2) may increase the antibody response to influenza virus vaccine inactivated in geriatric adults.

#### **■ Anticoagulants**

Prolonged prothrombin time, GI bleeding, transient gross hematuria, muscular hematoma, and epistaxis have been reported rarely in patients stabilized on warfarin sodium who were vaccinated with influenza virus vaccine inactivated. Although there have been conflicting reports on whether influenza virus vaccine inactivated can inhibit the metabolism or clearance of warfarin, most studies have failed to show any clinically important adverse effects of administration of the vaccine in anticoagulated patients. In addition, in at least one study, there was no evidence of clinically important local reactions at the site of IM injection (the deltoid region) when adequate local pressure

was applied after injection. The Advisory Committee on Immunization Practices (ACIP) and others state that administration of influenza virus vaccine inactivated is not contraindicated in patients receiving anticoagulants. Nonetheless, some clinicians suggest that patients receiving warfarin be monitored closely for possible enhanced anticoagulant effects in the immediate period following administration of influenza virus vaccine inactivated.

### ■ Antiviral Agents

Amantadine, rimantadine, and zanamivir do not appear to interfere with the antibody response to influenza virus vaccine inactivated. Although drug interaction studies have not been conducted to evaluate the immune response to influenza virus vaccine inactivated in patients receiving oseltamivir, oseltamivir therapy does not appear to impair normal humoral antibody response to infection in patients with naturally or experimentally acquired influenza. These antiviral agents may be used in conjunction with influenza virus vaccine inactivated if indicated.

### ■ Aspirin

There is some evidence that aspirin may increase the antibody response to influenza virus vaccine inactivated in geriatric adults.

### ■ Immune Globulins

There is no evidence that immune globulins (immune globulin IM [IGIM], immune globulin IV [IGIV]) or specific immune globulins (hepatitis B immune globulin [HBIG], rabies immune globulin [RIG], tetanus immune globulin [TIG], varicella zoster immune globulin [VZIG]) interfere with the immune response to inactivated vaccines. ACIP states that influenza virus vaccine inactivated may be given simultaneously with (using different syringes and different injection sites) or at any interval before or after immune globulin preparations.

### ■ Immunosuppressive Agents

Individuals receiving immunosuppressive therapy (e.g., corticotropin, corticosteroids, alkylating agents, antimetabolites, radiation therapy) may have a diminished immunologic response to influenza virus vaccine inactivated. Although corticosteroids administered for brief periods or every other day reportedly have only a minimal effect on antibody response to influenza virus vaccine inactivated, prolonged administration of high-dose corticosteroid therapy (i.e., a daily dosage equivalent to 2 mg/kg or greater or a total daily dosage of 20 mg of prednisone) may impair antibody response to the vaccine. Administration of influenza virus vaccine inactivated can be deferred temporarily during short-term, high-dose corticosteroid therapy, provided deferral does not compromise the likelihood of immunization before the start of the influenza season. However, long-term immunosuppressive therapy (e.g., corticosteroids in patients with chronic pulmonary disease) should not preclude vaccination in patients at risk for influenza since such patients may develop an adequate response and therefore could benefit from vaccination.

If influenza virus vaccine inactivated is used in patients receiving immunosuppressive therapy, the possibility that the expected antigenic response to the vaccine may not be attained should be considered. There is some evidence that administration of a booster dose of influenza virus vaccine inactivated (e.g., several weeks after the initial dose) may not improve immune response in patients receiving immunosuppressive therapy (e.g., transplant recipients). However, in a study in adults receiving chemotherapy for lymphoma, there was evidence that administration of a booster dose of the vaccine between chemotherapy courses could enhance vaccine response in many patients who responded inadequately to the first vaccine dose.

The American Academy of Pediatrics (AAP) states that children with malignant neoplasms who must undergo chemotherapy should be vaccinated 3 or more weeks after chemotherapy is discontinued and when peripheral granulocyte and lymphocyte counts are greater than 1000/mL. ACIP states that hematopoietic stem cell transplantation (HSCT) recipients should be revaccinated with influenza inactivated vaccine at least 6 months after HSCT and annually thereafter for the life of the patient.

### ■ Phenytoin

Various effects on serum phenytoin concentrations (i.e., both increases and decreases in total and/or free serum concentrations or no change) have been reported following influenza vaccination. Although most studies have failed to find a clinically important effect, the possibility of an interaction should be considered.

### ■ Theophylline

Influenza virus vaccine inactivated may inhibit clearance of theophylline. Although studies have failed to show a clinically important interaction, some manufacturers recommend that clinicians consider a possible interaction in individuals receiving theophylline.

### ■ Vaccines

Although specific studies may not be available evaluating concurrent administration with each antigen, simultaneous administration with other age-appropriate vaccines, including live virus vaccines, toxoids, or inactivated or recombinant vaccines, during the same health-care visit is not expected to affect the immunologic response or adverse reactions to any of the preparations. Immunization with influenza virus vaccine inactivated can be integrated with immunization against diphtheria, tetanus, pertussis, *Haemophilus influenzae* type b (HIB), hepatitis A, hepatitis B, human papillomavirus (HPV), poliovirus, measles, mumps, rubella, rotavirus, meningococcal disease, pneumococcal disease, and varicella. However, each vaccine should be administered using a different syringe and different injection site.

## Influenza Vaccines

ACIP states that seasonal influenza virus vaccine inactivated may be administered simultaneously with influenza A (H1N1) 2009 monovalent vaccine inactivated using different anatomic sites.

Data are not available to date regarding concomitant administration of seasonal influenza virus vaccine inactivated and influenza A (H1N1) 2009 monovalent vaccine live intranasal.

## Pneumococcal Vaccines

Influenza virus vaccine inactivated may be administered concomitantly with pneumococcal 23-valent polysaccharide vaccine (PPSV23; Pneumovax<sup>®</sup> 23) without a decrease in the antibody response or an increase in adverse reactions to the vaccines. The target groups for influenza vaccine and PPSV23 overlap considerably. For individuals who are at high risk but have not previously received pneumococcal 23-valent polysaccharide vaccine, ACIP and others recommend that concurrent administration of influenza virus vaccine inactivated and PPSV23 be strongly considered to ensure that both vaccines are administered. It should be emphasized, however, that influenza virus vaccine inactivated must be given annually, whereas PPSV23 generally is given only once, although revaccination may be indicated in some individuals. If influenza virus vaccine inactivated is administered concomitantly with PPSV23, the vaccines should be administered in separate syringes and into different extremities. Although there have been some reports of an increased incidence of adverse local and systemic effects when influenza virus vaccine was administered concomitantly with PPSV23 (at a different injection site) compared with administration of influenza vaccine alone, these reactions generally are mild and well tolerated and do not preclude simultaneous administration of the vaccines at different sites.

Influenza virus vaccine inactivated may be administered concomitantly with pneumococcal 7-valent conjugate vaccine (PCV7; Prevnar<sup>®</sup>).

## Zoster Vaccine

Influenza virus vaccine inactivated may be administered concomitantly (using different syringes and different injection sites) or at any interval before or after zoster vaccine live (ZOS).

Data from a randomized, placebo-controlled study in adults 50 years of age or older indicate that concurrent administration of influenza virus vaccine inactivated and zoster vaccine live results in antibody responses and adverse effects similar to those reported when the vaccines are administered 4 weeks apart.

## Laboratory Test Interferences

There was some evidence from the 1991–1992 influenza season to suggest that seasonal influenza virus vaccine inactivated may have interfered with certain serologic tests for determination of antibodies to human immunodeficiency virus type 1 (HIV-1), human T-lymphotropic virus type I (HTLV-I; human T-cell leukemia virus type I; adult T-cell leukemia virus, ATL), and hepatitis C virus-encoded (HCV) antigen. This suggestion was based on reports of blood from certain donors repeatedly exhibiting false-positive results for presence of antibodies to these viruses when tested with enzyme-linked immunosorbent assays (ELISA, EIA) produced by Abbott Laboratories (i.e., Abbott HIVAB<sup>®</sup> HIV-1 EIA, Abbott HTLV-I<sup>®</sup> EIA, and Abbott HCV<sup>®</sup> EIA for the respective viruses). More specific confirmatory tests (e.g., Western blot for HIV-1 and HTLV-I, recombinant immunoblotting assay for anti-HCV antibody) usually were negative, although indeterminate results occasionally were reported. Based on donor records, a correlation between recent immunization with influenza virus vaccine inactivated and the false-positive reactions appeared to exist.

Although it had been suggested that influenza virus vaccine inactivated may have induced an early nonspecific (e.g., IgM-mediated) reactivity in serum and plasma in some vaccinees resulting in the false-positive tests, subsequent study indicates that the cluster of multiple false-positive serologic tests observed during 1991–1992 was most likely caused by inadequate specificity of the test kits employed at the time rather than by influenza virus vaccine. Subsequent availability of screening tests with improved sensitivity for HIV-1 and hepatitis C makes false-positive serologic tests for antibodies to these viruses unlikely in influenza vaccinees.

## Pharmacology

Influenza virus vaccines stimulate active immunity to influenza virus infection by inducing production of specific antibodies; protection is provided only against those strains of virus from which the vaccines are prepared and closely related strains.

In healthy young adults, seasonal influenza virus vaccine inactivated has been shown to induce rapidly and simultaneously both a systemic (i.e., in serum) and, to a lesser extent, local (i.e., in the upper respiratory tract) immune response.

Local mucosal immunity in the respiratory tract (e.g., in tonsils) confers the initial line of defense against influenza. It has been suggested that migration of activated B cells, particularly IgA-committed B cells, via lymphatic drainage from the injection site to the mucosal surfaces of the tonsils is responsible for the local immune response after influenza vaccination. It also has been suggested that stimulation of local secretory IgA antibodies may be proportionately greater following intranasal influenza vaccination compared with parenteral vaccination, potentially resulting in an increased and broad mucosal and systemic immune response with the intranasal route of vaccination. Intranasal influenza vaccination with a live, attenuated (cold-adapted) influenza virus vaccine also may provide greater cross-protection against variant strains, possibly secondary to superior mucosal IgA and T-cell-mediated immune responses, but

comparative trials employing parenteral vaccination with currently available inactivated vaccines are necessary to provide definitive information on relative protective efficacy. Cytotoxic T cells may be cross-reactive against different subtypes of influenza A because of their recognition of internal viral antigens expressed on the surfaces of infected cells that are shared among influenza A viruses, despite antigenic differences between the hemagglutinin molecules. The live, attenuated intranasal vaccine also may induce the production of more broadly cross-reactive humoral antibodies. Influenza-specific antibodies are predominantly IgG and IgM in serum and IgA in oral fluids.

Efficacy of seasonal influenza virus vaccine inactivated in preventing or attenuating illness is variable, depending principally on the age and immunocompetence of the vaccinee and on the degree of similarity between the virus strains included in the vaccine formulation and those circulating during the influenza season.

Although postvaccination antibody titers initially may remain stable (e.g., hemagglutination-inhibition [HI], IgG) or decrease (e.g., IgA) with repeated annual vaccination against seasonal influenza, prevaccination titers of HI, IgG, and IgA prior to the subsequent annual dose are increased overall. Thus, repeated annual vaccination against seasonal influenza results in an increase in and maintenance of antibodies to influenza A (H1N1) and (H3N2) strains over time, which is beneficial for protection of vaccinees. Even in individuals in whom a decrease in antibody titers occurs with repeated vaccination, an increase in avidity of the antibodies for influenza antigens could prevent a decline in immune competence. Although some (the Hoskins paradox) have suggested that there may be a decrease in vaccine efficacy in field studies (i.e., where the efficacy measure is morbidity and mortality rates during naturally occurring influenza outbreaks), a pooled analysis of single versus multiple vaccination in serologic (immune-response) and field studies found no evidence that repeated annual vaccination negatively affected the protective effect of the vaccine. In addition, annual vaccination against seasonal influenza is recommended because of the constant development of antigenic variants via antigenic drifts, which is the virologic basis for seasonal epidemics and the reason for annual review and periodic reformulation of the antigenic composition of influenza virus vaccine inactivated.

## ■ Influenza Virus and Infection

Influenza viruses are spread from person to person, principally through the coughing or sneezing of infected individuals in close proximity to an uninfected person. Influenza is spread by direct deposition of virus-laden large droplets onto mucosal surfaces of the upper-respiratory tract during close contact with an infected individual and also by direct inhalation of droplet nuclei and small-particle aerosols into the lower respiratory tract. The contribution of virus-contaminated hands or fomites to transmission of influenza is not known, but this is not the principal mode of transmission. The main reservoirs of influenza virus are infected individuals, and the period of greatest communicability is during the initial 3 days of illness; however, viral shedding can occur before symptomatic onset and for up to a week or longer after symptoms develop.

Uncomplicated influenza illness is characterized by the abrupt onset of constitutional and respiratory signs and symptoms (e.g., fever, myalgia, headache, malaise, nonproductive cough, sore throat, rhinitis). Among children, otitis media, nausea, and vomiting also are commonly reported with influenza illness. Respiratory illness caused by influenza is difficult to distinguish from illness caused by other respiratory pathogens on the basis of symptoms alone, and laboratory testing can aid in diagnosis. Uncomplicated influenza illness typically resolves after 3–7 days for the majority of persons, although cough and malaise can persist for longer than 2 weeks. Influenza can also exacerbate chronic conditions (e.g., pulmonary or cardiac disease), and/or lead to secondary bacterial pneumonia, sinusitis, or otitis media; or contribute to coinfections with other viral or bacterial pathogens. Influenza-related deaths can result from pneumonia, as well as from exacerbations of cardiopulmonary conditions and other chronic diseases.

Influenza viruses can cause disease among persons in any age group, but rates of infection are highest among children. In temperate climates, seasonal epidemics of influenza generally occur during the winter months on an annual or near-annual basis. Rates of serious illness and death are highest among adults 65 years of age and older, children younger than 2 years of age, and individuals of any age who have medical conditions that place them at increased risk for complications from influenza. An annual average of approximately 36,000 deaths during 1990–1999 and 226,000 hospitalizations during 1979–2001 has been associated with influenza epidemics. The typical incubation period for seasonal influenza is 1–4 days (average: 2 days). Adults shed influenza virus from the day before symptoms begin through 5–10 days after illness onset. However, the amount of virus shed, and presumably, infectivity decreases rapidly by 3–5 days after onset in an experimental human infection model. Young children also might shed virus several days before illness onset, and children can be infectious for 10 days or more after onset of symptoms. Severely immunocompromised persons can shed virus for weeks or months.

## ■ Antigenic Characteristics of Influenza Viruses

Influenza A viruses are classified into subtypes based on 2 surface antigens, hemagglutinin (H) and neuraminidase (N). Three subtypes of hemagglutinin (H1, H2, H3) and 2 subtypes of neuraminidase (N1 and N2) have been identified among influenza A viruses that have caused widespread disease in humans, although H2 generally has been absent from human circulation for many years. Immunity to these antigens, especially hemagglutinin, reduces the likelihood of infection and the severity of disease if an individual does become infected. However, there may be sufficient antigenic variation (antigenic *drift*) within the same subtype over time, so that infection or vaccination with one strain may not induce immunity to distantly related strains of the

same subtype. Influenza B viruses also demonstrate antigenic variation, although less rapidly and to a lesser extent than influenza A viruses. Circulating influenza B viruses are separated into 2 distinct genetic lineages (Yamagata and Victoria); however, unlike influenza A viruses, influenza B viruses are not divided into subtypes. Because of the antigenic variation associated with both influenza A and B viruses, major epidemics of respiratory disease caused by new variants of influenza virus continue to occur, usually at 1- to 3-year intervals. Therefore, the antigenic characteristics of current strains of seasonal influenza virus identified by ongoing surveillance are used as the basis for selecting influenza virus strains to be included in each year's seasonal influenza vaccine.

The current practice of surveillance and periodic incorporation of new antigenic variants into the annual seasonal vaccine formulation generally has been effective in addressing antigenic *drifts* in the virus. Although it has been suggested that development of vaccines that are more potent than those available may overcome antigenic *drifts*, especially for influenza type A (H3N2) viruses, some evidence suggests that this would not be the case since higher potency vaccines do not appear to increase antibody response substantially. Of additional concern are antigenic *shifts* in which major changes (e.g., by more than 50%) in the nucleotide sequence of the hemagglutinin or neuraminidase occur, since such shifts have the potential for causing pandemics. Fortunately, such shifts occur far less frequently than antigenic drifts; however, they also are less predictable, and while only 3 hemagglutinin subtypes have been known to infect humans until 1997, it appears that at least 15 such subtypes exist.

During 2009, cases of human infection with a new influenza A (H1N1) virus, previously referred to as the novel 2009 influenza A (H1N1) virus or swine-origin influenza A (H1N1), were reported in several countries, including the US. This virus contains a unique combination of gene segments not previously reported among human or swine influenza A in the US or elsewhere and appears to be a triple-reassortant swine influenza virus containing genes from human, swine, and avian influenza A viruses. On June 11, 2009, the WHO declared that the first global influenza pandemic in 41 years was occurring and issued a phase 6 pandemic alert regarding 2009 influenza A (H1N1). (See Uses: Pandemic Influenza.)

There also are influenza A subtypes that occur mainly in birds but also have rarely caused infection in humans (H5N1, H7N2, H7N3, H7N7, H9N2). Future epidemics or pandemics could involve avian influenza viruses or new influenza subtypes, and monitoring avian and animal populations and humans closely associated with poultry and animals provides important information regarding new strains. (See Pandemic Influenza under Uses: Management of Exposure.)

## *Antigenic Drifts during Recent Years*

During the 2003–2004, 2004–2005, and 2005–2006 influenza seasons, influenza A (H1N1), A (H3N2), and B viruses all circulated widely; influenza A (H3N2) viruses predominated. During the 2006–2007 influenza season, influenza A (H1N1) predominated. During the 2007–2008 influenza season, a drifted influenza A (H3N2) virus and an influenza B strain from a different lineage than that used in the 2007–2008 vaccine formulation were reported.

During both the 2007–2008 and 2008–2009 influenza seasons, influenza A (H1N1), influenza A (H3N2), and influenza B viruses cocirculated and, although more influenza A viruses than influenza B viruses were identified overall, the relative proportion of influenza B viruses increased during February and March.

### **Influenza Type A (H1N1).**

Most influenza A (H1N1) isolated worldwide during the 2005–2006 influenza season were antigenically similar to the A/New Caledonia/20/99 strain contained in the annual seasonal influenza vaccine. Therefore, FDA, WHO, and NACI recommended that the A/New Caledonia/20/99-like strain be retained in the 2006–2007 seasonal vaccine.

Although most influenza A (H1N1) isolated worldwide during the 2006–2007 influenza season were similar to A/New Caledonia/20/99A, isolates that were similar to A/Solomon Islands/3/2006 (an antigenic variant of A/New Caledonia/20/99) were identified late in the season. FDA, WHO, and NACI recommended that the A (H1N1) component for the 2007–2008 seasonal influenza vaccine be changed to an A/Solomon Islands/3/2006-like strain (manufacturers for the US market used the A/Solomon Islands/3/2006 strain itself).

During the 2007–2008 influenza season, most influenza A (H1N1) viruses were characterized as A/Solomon Islands/3/2006-like and were closely related to the influenza A (H1N1) component of the 2007–2008 seasonal influenza vaccine. However, an increasing proportion were antigenically distinguishable from the vaccine strains and more closely related to A/Brisbane/59/2007. Therefore, FDA, WHO, and NACI recommended that an A/Brisbane/59/2007-like strain be used for the influenza A (H1N1) component of 2008–2009 seasonal influenza vaccines used in the northern hemisphere.

During the 2008–2009 influenza season, the majority of circulating seasonal influenza A (H1N1) viruses were related to the influenza A (H1N1) component of the 2008–2009 seasonal influenza vaccine (A/Brisbane/59/2007). Therefore, FDA and WHO recommended that an A/Brisbane/59/2007-like strain be retained for the influenza A (H1N1) component of the 2009–2010 seasonal influenza vaccines used in the northern hemisphere.

### **Influenza Type A (H3N2).**

During the 2004–2005 season, 22% of influenza A isolates (H3N2) were related antigenically to A/Wyoming/3/2003 (the A/Fujian/411/2002-like component of the 2004–2005 vaccine) and 78% were antigenically related to A/California/07/2004. The US Food and Drug Administration (FDA), the World Health Organization (WHO), and

the Canadian National Advisory Committee on Immunization (NACI) recommended that an A/California/07/2004-like virus be used for the influenza A (H3N2) component of the 2005–2006 influenza virus vaccine. Manufacturers for the US market used the antigenically equivalent A/New York/55/2004 strain for this component.

During the 2005–2006 season, 75.7% of influenza A isolates (H3N2) were related antigenically to A/California/07/2004 but an increasing proportion of isolates were related to A/Wisconsin/67/2005. FDA, WHO, and NACI recommended that an A/Wisconsin/67/2005-like virus be used for the influenza A (H3N2) component of the 2006–2007 influenza virus vaccine. Manufacturers could use the antigenically equivalent A/Hiroshima/52/2005 virus for this component.

Antigenic characteristics of isolates of influenza A (H3N2) circulating worldwide during the 2006–2007 season indicated that most were antigenically related to A/Wisconsin/67/2005 and A/Hiroshima/52/2005 (components of the 2006–2007 influenza virus vaccine). An increasing proportion of isolates late in the season differed both genetically and antigenically from the vaccine strain; however, antigenic analysis did not reveal the emergence of a sufficiently well characterized variant group. Beginning in late February 2007, most influenza A (H3) isolates in the US showed reduced titers with antisera produced against A/Wisconsin/67/2005. WHO stated that while genetic variation was observed during the 2006–2007 season, the absence of a sufficiently well characterized antigenically variant group (including the lack of corresponding egg isolates) precluded the selection of a new vaccine candidate in time for the 2007–2008 influenza season. FDA, WHO, and NACI recommended that an A/Wisconsin/67/2005-like virus be used for the influenza A (H3N2) component of the 2007–2008 influenza virus vaccine. Manufacturers used the antigenically equivalent A/Hiroshima/52/2005 virus for this component. Manufacturers for the US market used the A/Wisconsin/67/2005 strain itself.

During the 2007–2008 influenza season, 22% of influenza A (H3N2) viruses tested by the CDC were characterized as A/Wisconsin/67/2005-like, the influenza A (H3N2) component of the 2007–2008 influenza vaccine for the northern hemisphere, and 71% were characterized as A/Brisbane/10/2007-like. The A/Brisbane/10/2007-like strains are recent antigenic variants of A/Wisconsin/67/2005-like strains. Therefore, FDA, WHO, and NACI recommended that an A/Brisbane/10/2007 strain be used for the influenza A (H3N2) component of 2008–2009 influenza virus vaccines used in the northern hemisphere.

During the 2008–2009 influenza season, the majority of circulating influenza A (H3N2) viruses were related to the influenza A (H3N2) component of the 2008–2009 seasonal influenza vaccine (A/Brisbane/10/2007 and A/Uruguay/716/2007). Therefore, FDA and WHO recommended that an A/Brisbane/10/2007-like strain be retained for the influenza A (H3N2) component of the 2009–2010 seasonal influenza vaccines used in the northern hemisphere.

#### **Influenza Type B.**

During the 2004–2005 season, most influenza B viruses (75%) belonged to the B/Yamagata/16/88 lineage and were antigenically similar to B/Sichuan/361/2002; some B viruses (25%) belonged to the B/Victoria/2/87 lineage. The B component of the 2004–2005 influenza vaccine (B/Shanghai/361/2002-like) belongs to the B/Yamagata lineage. FDA, WHO, and NACI recommended that a B/Shanghai/361/2002-like virus be retained for the influenza B component for the 2005–2006 vaccine. Antigenically equivalent strains such as B/Jiangsu/10/2003 and B/Jilin/20/2003 could be used. Because of the growth properties of B/Jiangsu/10/2003, manufacturers for the US market used this strain as the B component of the 2005–2006 influenza virus vaccine.

During the 2005–2006 season, most influenza B viruses (78.1%) belonged to the B/Victoria lineage which was not covered by the 2005–2006 vaccine. FDA, WHO, and NACI recommended that a B/Malaysia/2506/2004-like virus (belonging to the B/Victoria lineage) be used for the influenza B component for the 2006–2007 vaccine. Manufacturers could use the antigenically equivalent B/Ohio/1/2005 virus for this component.

During the 2006–2007 season, most influenza B viruses were similar to Malaysia/2506/2004. FDA, WHO, and NACI recommended that a B/Malaysia/2506/2004-like virus be used for the influenza B component for the 2007–2008 vaccine. Manufacturers for the US market used the Malaysia/2506/2004 strain itself.

During the 2007–2008 season, influenza B viruses of both the B/Victoria/2/87 and B/Yamagata/16/88 lineages continued to circulate in the US and worldwide, but most were of the B/Yamagata lineage and were antigenically distinct from the B/Malaysia/2506/2004-like component of the 2007–2008 vaccine. Influenza surveillance in Canada indicated that the proportion of A/Brisbane/10/2007-like strains steadily increased over the 2007–2008 season. WHO reported that many viruses of the B/Victoria/2/87 lineage were closely related to the 2007–2008 vaccine virus B/Malaysia/2506/2004, but an increase in antigenic heterogeneity was observed, and most strains identified late in the season were antigenically similar to B/Florida/04/2006. Therefore, FDA, WHO, and NACI recommended that a B/Florida/04/2006-like strain be used for the influenza B component of 2008–2009 influenza vaccines used in the northern hemisphere.

During the 2008–2009 influenza season, influenza B viruses of both the B/Victoria/2/87 and the B/Yamagata/16/88 lineages continued to circulate in the US and worldwide. However, strains related to the B/Victoria lineage predominated. Less than 20% of circulating influenza B strains during the 2008–2009 influenza season were of the B/Yamagata lineage and were related to the influenza B component used in the 2008–2009 seasonal influenza vaccine (B/Florida/04/2006). Most circulating influenza

B strains (more than 80%) belonged to the B/Victoria lineage and were not covered by the strain used in the 2008–2009 vaccine. Therefore, the FDA and WHO recommended that the influenza B component of the 2009–2010 seasonal influenza vaccine be changed to a B/Brisbane/60/2008-like strain (B/Victoria lineage).

### **■ Response to Seasonal Influenza Virus Vaccine Inactivated *Adults Younger than 65 Years of Age***

Following administration of seasonal influenza virus vaccine inactivated, a protective effect generally is achieved in 70–90% of healthy adults younger than 65 years of age who receive the vaccine, usually within 10–14 days, when there is a good antigenic match between vaccine formulation and circulating strains.

Potency of seasonal influenza vaccines is such that most healthy young adults who receive the vaccines develop high post-vaccination hemagglutination-inhibition (HI) antibody titers that are likely to protect them against illness by strains like those in the vaccine and may also protect against illness by related variants. However, when compared with healthy, young adults, patients with certain chronic diseases may develop lower postvaccination antibody titers and may remain susceptible to influenza-related upper respiratory tract infection.

#### ***Geriatric Adults***

Geriatric individuals, particularly those who are institutionalized, may develop lower postvaccination antibody titers than do healthy, young adults.

Efficacy of seasonal influenza virus vaccine inactivated in preventing hospitalization for pneumonia and influenza has been reported to range from 27–70% among geriatric individuals residing outside nursing homes or similar chronic-care facilities. In geriatric individuals residing in chronic-care facilities, the vaccine usually is 20–40% effective in preventing acute respiratory illness and 80% effective in preventing death. Achieving high rates of vaccination in chronic-care facilities can reduce the risk of an influenza outbreak.

In 3 case-control studies conducted as part of a seasonal influenza virus vaccine demonstration project among Medicare beneficiaries (i.e., geriatric individuals), the aggregate estimated efficacy of vaccination in preventing hospitalization for pneumonia was 31–45% during the 1989–90, 1990–91, and 1991–92 influenza seasons. In a large cohort study in geriatric individuals (65 years of age and older) living in the community, influenza vaccination during epidemic and nonepidemic years was associated with a 48–57% reduction in the hospitalization rate for pneumonia and influenza and in 27–39 and 37% reductions in the rates of hospitalization for acute and chronic respiratory conditions and for congestive heart failure, respectively. Vaccination also was associated with a 39–54% reduction in all-cause mortality in this geriatric population during the last 3 influenza seasons (1990–1993) of the cohort study. Pooled data from this study and subsequent continued study for 3 additional influenza seasons (1993–1996) showed that seasonal influenza vaccination was associated with overall (over all 6 seasons) reductions in hospitalizations for pneumonia, all respiratory conditions, and congestive heart failure of 39, 32, and 27% respectively, and in all-cause mortality of 50%. This study also confirmed that both healthy geriatric adults and those with underlying medical conditions are at risk for serious complications of influenza and benefit from vaccination.

#### ***Children and Adolescents***

Children as young as 6 months of age usually can develop protective levels of antibody after vaccination with seasonal influenza virus vaccine inactivated. However, the inactivated vaccine is less immunogenic in children younger than 6 months of age than in children 6–18 months of age and the antibody response might be lower among children at high risk of influenza infection than among healthy children. (See Cautions: Pediatric Precautions.)

Vaccine efficacy is lower in previously unvaccinated children younger than 9 years of age who have received only 1 dose of vaccine compared with children who have received 2 doses of vaccine.

#### ***Immunocompromised Individuals***

The response to seasonal influenza virus vaccine inactivated in individuals with immunodeficiencies or in individuals receiving immunosuppressive therapy generally is less than that in healthy individuals. There is some evidence that administration of a second (i.e., booster) dose of the vaccine may not improve immune response in immunosuppressed individuals (e.g., transplant recipients receiving immunosuppressive drugs, human immunodeficiency virus [HIV]-infected individuals). However, in a study in adults receiving chemotherapy for lymphoma, there was evidence that a second dose of the vaccine could enhance immunologic response in many patients who responded inadequately to the first vaccine dose.

##### **HIV-infected Individuals.**

Vaccine-induced antibody levels generally are lower in individuals with HIV infection than in healthy individuals and may be inversely correlated with the severity of manifestations associated with HIV infection. Seasonal inactivated influenza vaccine has induced protective antibody titers in HIV-infected children and adults who had only minimal acquired immunodeficiency syndrome (AIDS)-related symptoms and mean CD4<sup>+</sup> T-cell counts of 400/mm<sup>3</sup>. In those with advanced disease and low CD4<sup>+</sup> T-cell counts (e.g., less than 100/mm<sup>3</sup>), the vaccine may not induce adequate antibody titers, and a booster dose (e.g., administered 4 or more weeks after the first dose) of the vaccine does not appear to improve the immune response in such individuals.

Some evidence indicates that the antibody response to seasonal influenza virus vaccine inactivated correlates directly with the CD4<sup>+</sup> T-cell count and inversely with

the plasma HIV-1 RNA level, being particularly impaired with CD4<sup>+</sup> counts less than 100/mm<sup>3</sup> and HIV-1 RNA levels exceeding 100,000 copies/mL. In one study in men, administration of influenza virus vaccine inactivated resulted in protective levels of hemagglutination-inhibiting (HI) antibodies (i.e., 1:64 or greater) in 71–100% of those seronegative for HIV antibodies, 32–89% of those with asymptomatic HIV infection, and 13–54% of those with AIDS or AIDS-related complex (ARC). In several other studies in HIV-infected adults, almost no HI antibodies were measurable in those with CD4<sup>+</sup> T-cell counts less than 100/mm<sup>3</sup>, and counts of 100–300/mm<sup>3</sup> correlated with a suboptimal antibody response; those with T-cell counts of 300 or more per mm<sup>3</sup> were most likely to develop protective titers. Results of a small, randomized, placebo-controlled study indicate that influenza virus vaccine is highly effective in preventing symptomatic, laboratory-confirmed influenza infection among HIV-infected individuals with mean CD4<sup>+</sup> T-cell counts of 400/mm<sup>3</sup>.

Some studies have shown transient (e.g., 2- to 4-week) increases in the replication of HIV type 1 (HIV-1) in plasma and mononuclear cells of HIV-infected individuals following seasonal influenza vaccination, particularly in those who exhibited an antibody response to the vaccine and were not receiving suppressive antiretroviral therapy, and it has been suggested that continued antigenic stimulation by repeated vaccination could result in an increased HIV viral load. However, other studies employing similar laboratory techniques have not confirmed these findings, and there currently is no convincing evidence that seasonal influenza virus vaccine inactivated results in long-term adverse consequences on CD4<sup>+</sup> T-cell counts or progression of clinical HIV disease in HIV-infected individuals. In addition, any transient increases in HIV replication that do occur appear to be associated with an effect on disease progression that is so minimal that it is difficult to detect. Some evidence suggests that the humoral response to influenza antigens is improved in HIV-infected individuals treated with highly active antiretroviral therapy.

#### ■ Duration of Immunity

The duration of immunity declines during the year after vaccination with seasonal inactivated influenza vaccine. Since circulating strains of influenza virus change from year to year, annual vaccination with seasonal influenza vaccine is needed.

Vaccine from a previous influenza season (e.g., 2008–2009) should not be used in an attempt to provide protection during a subsequent influenza season (e.g., 2009–2010).

## Chemistry and Stability

### ■ Chemistry

Inactivated influenza virus vaccines used for prevention of seasonal influenza are trivalent vaccines containing noninfectious, sterile suspensions of suitably inactivated influenza virus types A and B subunits. Seasonal inactivated influenza virus vaccines are prepared from formaldehyde- or propiolactone-inactivated influenza viruses harvested from allantoic fluids of chick embryos infected with the viruses and are commercially available in the US as split-virus preparations (purified subvirion or purified surface antigen). Subvirion inactivated influenza virus vaccines are prepared by chemically disrupting the inactivated viruses to smaller subunit particles before purifying and suspending them in a phosphate-buffered, isotonic sodium chloride solution. Purified surface antigen inactivated influenza virus vaccines are prepared by purifying the inactivated viruses, chemically removing the surface antigens from the internal proteins of the viruses, and purifying and suspending the surface antigens in a phosphate-buffered, isotonic sodium chloride solution.

Inactivated influenza virus vaccines used for prevention of seasonal influenza are formulated annually. Vaccines commercially available in the US and Canada are formulated as specified by the US Food and Drug Administration Vaccines and Related Biological Products Advisory Committee (VRBPAC) and Canadian National Advisory Committee on Immunization (NACI), respectively, and generally contain 3 antigens (usually from two type A and one type B virus strains) representative of the strains of influenza virus that are likely to circulate in the US and Canada in the upcoming influenza season. Similarly, the World Health Organization (WHO) annually recommends the composition of influenza virus vaccines. Recommendations are based on antigenic analyses of recently isolated influenza viruses, epidemiologic data, postvaccination serologic studies in humans, and the availability of candidate vaccine strains and reagents. For the 2009–2010 season, the antigenic components recommended for the US formulation are the same as those recommended by WHO (northern hemisphere). The US vaccines meet standards established by the Center for Biologics Evaluation and Research of the US Food and Drug Administration, and potency meets requirements of the specific radial-immunodiffusion tests for hemagglutinin based on comparison with the US reference influenza virus vaccine inactivated.

Influenza virus vaccine inactivated 2009–2010 occurs as a clear and/or slightly opalescent solution after vigorous shaking. Afluria<sup>®</sup> is commercially available in 0.5-mL prefilled syringes as a preservative-free formulation (thimerosal was not used in the manufacturing process) and in multiple-dose vials that contain thimerosal as a preservative (24.5 mcg of mercury per 0.5-mL dose). Fluvirin<sup>®</sup> is commercially available in the US in multiple-dose vials that contain thimerosal as a preservative (25 mcg of mercury per 0.5-mL dose). Fluvirin<sup>®</sup> also is commercially available in 0.5-mL prefilled syringes as a preservative-free formulation that contains only trace amounts of thimerosal from the manufacturing process (less than 1 mcg of mercury per 0.5-mL

dose). Fluarix<sup>®</sup> is commercially available in 0.5-mL prefilled syringes as a preservative-free formulation that does not contain thimerosal. Fluzone<sup>®</sup> is commercially available in 0.25- and 0.5-mL prefilled syringes and in a 0.5-mL vial as a preservative-free formulation (thimerosal was not used in the manufacturing process) and in multiple-dose vials as a formulation containing thimerosal as a preservative (25 mcg of mercury per 0.5-mL dose). FluLaval<sup>®</sup> is commercially available in multiple-dose vials as a formulation containing thimerosal as a preservative (25 mcg of mercury per 0.5-mL dose).

### Composition of 2009–2010 Influenza Virus Vaccine Inactivated

The US Food and Drug Administration (FDA) Vaccines and Related Biological Products Advisory Committee (VRBPAC) recommended that the 2009–2010 trivalent influenza vaccine for the US contain A/Brisbane/59/2007-like (H1N1), A/Brisbane/10/2007-like (H3N2), and B/Brisbane/60/2008-like viruses. Only 1 of 3 antigens in the 2009–2010 seasonal vaccine (the influenza B component) differs from the antigens contained in the 2008–2009 trivalent influenza vaccine. The antigens were selected based on antigenic analysis of influenza viruses circulating worldwide, antibody responses reported for individuals who received the 2008–2009 vaccine, and the availability of candidate vaccine strains and reagents. Each 0.5-mL dose of influenza virus vaccine inactivated 2009–2010 commercially available in the US contains 15 mcg hemagglutinin of each of the following 3 antigens: A/Brisbane/59/2007, IVR-148 (H1N1); A/Uruguay/716/2007, NYMC X-175C (H3N2) (A/Brisbane/10/2007-like); and B/Brisbane/60/2008.

#### Influenza Type A (H1N1) Component.

During the 2008–2009 influenza season, all of the seasonal influenza A (H1N1) strains submitted to the Centers for Disease Control and Prevention (CDC) for antigenic testing were characterized as A/Brisbane/59/2007-like, the influenza A (H1N1) component of the 2008–2009 influenza vaccine. In addition, WHO data indicated that the majority of influenza A (H1N1) viruses circulating worldwide were closely related to the vaccine strain A/Brisbane/59/2007. Therefore, FDA and WHO recommended that an A/Brisbane/59/2007-like strain be used for the influenza A (H1N1) component of the 2009–2010 seasonal influenza virus vaccine.

#### Influenza Type A (H3N2) Component.

During the 2008–2009 influenza season, all seasonal influenza A (H3N2) viruses collected in the US and submitted to the CDC were related to the A/Brisbane/10/2007-like strains included in the 2008–2009 season. Likewise, WHO data indicated that the majority of worldwide H3N2 strains were closely related to A/Brisbane/10/2007. Therefore, FDA and WHO recommended that an A/Brisbane/10/2007-like strain be used for the influenza A (H3N2) component of the 2009–2010 seasonal influenza virus vaccine.

#### Influenza Type B Component.

During the 2008–2009 season, influenza B viruses of both the B/Victoria/02/87 and the B/Yamagata/16/88 lineages continued to circulate in the US and worldwide, but most were of the B/Victoria/02/87 lineage and were antigenically distinct from the B component of the 2008–2009 vaccine (B/Florida/04/2006-like). Therefore, FDA and WHO recommended that a B/Brisbane/60/2008-like strain be used for the influenza B component of the 2009–2010 influenza vaccine.

### Antigenic Composition of 2009–2010 Inactivated Vaccine for Prevention of Seasonal Influenza

Component	Strains to Be Covered	Strain Used
Influenza type A (H1N1)	those similar to A/Brisbane/59/2007	A/Brisbane/59/2007
Influenza type A (H3N2)	those similar to A/Brisbane/10/2007	A/Uruguay/716/2007
Influenza type B	those similar to B/Brisbane 60/2008	B/Brisbane/60/2008

### ■ Stability

Influenza virus vaccine inactivated for prevention of seasonal influenza should be refrigerated at 2–8°C and should not be frozen. If freezing occurs, the vaccine should be discarded because the potency of the vaccine is destroyed by freezing.

In between uses, multiple-dose vials should be returned to 2–8°C. The vaccine should be discarded if not used by the expiration date noted on the vial.

Influenza virus vaccine inactivated should be protected from light.

Depending on the manufacturer, single-dose syringes and vials are preservative-free or contain only trace amounts of thimerosal from the manufacturing process. Multiple-dose vials contain thimerosal as a preservative. (See Thimerosal Precautions under Cautions: Precautions and Contraindications.)

When stored as directed, inactivated influenza virus vaccines have an expiration date not later than 18 months after the date of issue from the manufacturer's cold storage (e.g., 1 year when the manufacturer's cold storage was 5°C).

Any remaining influenza virus vaccine inactivated 2008–2009 from the previous influenza season should not be used for the 2009–2010 season.

## Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

### **Influenza Virus Vaccine Inactivated (2009–2010)**

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#### **Parenteral**

Injectable suspension, for IM use

15 mcg hemagglutinin each of  
A/Brisbane/59/2007 (H1N1), A/  
Uruguay/716/2007 (H3N2) (A/  
Brisbane/10/2007-like), and B/  
Brisbane/60/2008 per 0.5 mL

**Afluria**<sup>®</sup> (preservative-free; available in 0.5 mL prefilled disposable syringes or with thimerosal [24.5 mcg of mercury per 0.5 mL]; available in multiple-dose vials), CSL Biotherapies

**Fluarix**<sup>®</sup> (preservative-free ; available in 0.5 mL prefilled disposable syringes), GlaxoSmithKline

**FluLaval**<sup>®</sup> (with thimerosal [25 mcg of mercury per 0.5 mL]; available in multiple-dose vials), GlaxoSmithKline

**Fluvirin**<sup>®</sup> (preservative-free with thimerosal [ $<1$  mcg of mercury per 0.5 mL]; available in 0.5 mL prefilled disposable syringes or with thimerosal [25 mcg of mercury per 0.5 mL]; available in multiple-dose vials), Novartis Vaccines

**Fluzone**<sup>®</sup> (preservative-free; available in 0.25 mL prefilled disposable syringes, 0.5 mL prefilled disposable syringes, and 0.5 mL vials or with thimerosal [25 mcg of mercury per 0.5 mL]; available in multiple-dose vials), Sanofi Pasteur