AHFS Category 80:12

Influenza Virus Vaccine
Fluzone®

℞ only

2003 – 2004 Formula

DESCRIPTION

Fluzone®, Influenza Virus Vaccine, (Zonal Purified, Subvirion) for intramuscular use, is a sterile suspension prepared from influenza viruses propagated in fertilized chicken eggs. The virus-containing fluids are harvested and inactivated with formaldehyde. Influenza virus is concentrated and purified in a linear sucrose density gradient solution using a continuous flow centrifuge. The virus is then chemically disrupted using a nonionic surfactant (Triton® X-100 – A registered trademark of Union Carbide, Co.) producing a "split-virus." The split-virus is then further purified by chemical means and suspended in sodium phosphate-buffered isotonic sodium chloride solution. Fluzone has been standardized according to USPHS requirements for the 2003–2004 influenza season and is formulated to contain 45 micrograms (µg) hemagglutinin (HA) per 0.5 mL dose, in the recommended ratio of 15 µg HA each, representative of the following three prototype strains: A/New Caledonia/20/99 (H1N1), A/Panama/2007/99 (H3N2) (an A/Moscow/10/99-like strain) and B/Hong Kong/1434/2002 (a B/Hong Kong/330/2001-like strain).[1] Gelatin 0.05% is added as a stabilizer. Fluzone is supplied in a unit dose preservative-free presentation distinguished by a pink syringe plunger rod in a 0.25 mL prefilled syringe (for pediatric use), formulated without preservatives but containing a trace amount of thimerosal [(contains 49.6% mercury), (≤ 0.5 µg Hg/0.25 mL dose) (≤ 1.0 µg Hg/0.5 mL dose)] from the manufacturing process. Fluzone is also supplied in two other presentations: a 0.5 mL prefilled syringe and 5 mL vial of vaccine, both of which contain the preservative thimerosal [(mercury containing compound), 25 µg mercury/0.5 mL dose]. Fluzone, after shaking syringe/vial well, is essentially clear and slightly opalescent in color.

ANTIBIOTICS ARE NOT USED IN THE MANUFACTURE OF FLUZONE.

CLINICAL PHARMACOLOGY

Epidemics of influenza typically occur during the winter months and were responsible for an average of approximately 36,000 deaths per year in the United States (US) during 1990–1999. Influenza viruses also can cause pandemics during which rates of illness and death from influenza-related complications can increase dramatically worldwide. Influenza viruses cause disease among all age groups. Rates of infection are highest among children, but rates of serious illness and death are highest among persons aged ≥ 65 years and persons of any age who have medical conditions that place them at increased risk for complications from influenza.[1]

Influenza vaccination is the primary method for preventing influenza and its severe complications. The primary target groups recommended for annual vaccination are 1) groups that are at increased risk for influenza-related complications (eg, persons aged ≥ 65 years and persons of any age with certain chronic medical conditions); 2) persons aged 50-64 years because this group has an elevated prevalence of certain chronic medical conditions; and 3) persons who live with or care for persons at high risk (eg, health-care workers and household members who have frequent contact with persons at high risk and who can transmit influenza to persons at high risk). Vaccination is associated with reductions in influenza-related respiratory illness and physician visits among all age groups, hospitalization and death among persons at high risk, otitis media among children, and work absenteeism among adults.[1]

Among persons aged ≥ 65 years, influenza vaccination levels increased from 33% in 1989 to 66% in 1999, surpassing the Healthy People 2000 goal of 60%. Although 1999 influenza vaccination coverage reached the highest levels recorded among black, Hispanic, and white populations, vaccination levels among blacks and Hispanics continue to lag behind those among whites.[1]

Increasing vaccination coverage among persons who have high-risk conditions and are aged < 65 years, including children at high risk, is the highest priority for expanding influenza vaccine use.[1]

Vaccination of health-care workers has been associated with reduced work absenteeism and fewer deaths among nursing home patients. Efforts should be made to educate health-care workers regarding the benefits of vaccination and the potential health consequences of influenza illness for themselves and their patients.[1]

Influenza A and B are the two types of influenza viruses that cause epidemic human disease.[1]

Influenza A viruses are further categorized into subtypes based on two surface antigens: hemagglutinin (H) and neuraminidase (N). Influenza B viruses are not categorized into subtypes. Both influenza A and B viruses are further separated into groups based on antigenic characteristics. New influenza virus variants result from frequent antigenic change (ie, antigenic drift), resulting from point mutations that occur during viral replication. Influenza B viruses undergo antigenic drift less rapidly than influenza A viruses. Since 1977, influenza A (H1N1) viruses, influenza A (H3N2) viruses, and influenza B viruses have been in global circulation. A person's immunity to the surface antigens, especially hemagglutinin, reduces the likelihood of infection and severity of disease if infection occurs. Antibody against one influenza virus type or subtype confers little or no protection against another virus. Furthermore, antibody to one antigenic variant of influenza virus might not protect against a new antigenic variant of the same type or subtype. Frequent development of antigenic variants through antigenic drift is the virological basis for seasonal epidemics and the reason for the usual incorporation of ≥ 1 new strains in each year's influenza vaccine.[1]

Formal subclassification utilizing neuraminidase antigens has not been done for influenza B viruses.

The incubation period for influenza is 1-4 days with an average of 2 days. Adults typically are infectious from the day before symptoms begin through approximately 5 days after illness onset. Children can be infectious for ≥ 10 days, and young children can shed virus for < 6 days before their illness onset. Severely immunocompromised persons can shed virus for weeks or months. Uncomplicated influenza illness is characterized by the abrupt onset of constitutional and respiratory signs and symptoms (eg, fever, myalgia, headache, severe malaise, nonproductive cough, sore throat, and rhinitis). Among children, otitis media, nausea and vomiting are also commonly reported with influenza illness. Influenza illness typically resolves after a limited number of days for the majority of persons, although cough and malaise can persist for > 2 weeks. Among certain persons, influenza can exacerbate underlying medical conditions (eg, pulmonary or cardiac disease), lead to secondary bacterial pneumonia or primary influenza viral pneumonia, or occur as part of a coinfection with other viral or bacterial pathogens. Young children with influenza infection can have initial symptoms mimicking bacterial sepsis with high fevers and < 20% of children hospitalized with influenza can have febrile seizures. Influenza infection has also been associated with encephalopathy, transverse myelitis, Reye syndrome, myositis, myocarditis, and pericarditis.[1]

The risks for complications, hospitalizations, and deaths from influenza are higher among persons aged ≥ 65 years, young children, and persons of any age with certain underlying health conditions than among healthy older children and younger adults.[1]

Among children aged 0-4 years, hospitalization rates have ranged from approximately 500/100,000 population for those with high-risk medical conditions to 100/100,000 population for those without high-risk medical conditions. Within the 0-4 age group, hospitalization rates are highest among children aged 0-1 years and are comparable to rates reported among persons aged ≥ 65 years.[1]

During influenza epidemics from 1969–1970 through 1994–1995, the estimated overall number of influenza-associated hospitalizations in the US has ranged from approximately 16,000 to 220,000/epidemic. An average of approximately 114,000 influenza-related excess hospitalizations occurred per year, with 57% of all hospitalizations occurring among persons aged < 65 years. Since the 1968 influenza A (H3N2) virus pandemic, the greatest numbers of influenza-associated hospitalizations have occurred during epidemics caused by type A (H3N2) viruses, with an estimated average of 142,000 influenza-associated hospitalizations per year.[1]

Influenza-related deaths can result from pneumonia as well as from exacerbations of cardiopulmonary conditions and other chronic diseases. Older adults account for ≥ 90% of deaths attributed to pneumonia and influenza. In a recent study of influenza epidemics, approximately 19,000 influenza-associated pulmonary and circulatory deaths per influenza season occurred during 1976–1990 compared with approximately 36,000 deaths per influenza season during 1990–1999. Estimated rates of influenza-associated pulmonary and circulatory deaths per 100,000 persons were 0.4-0.6 among persons aged 0-49 years, 7.5 among persons aged 50-64 years, and 98.3 among persons aged ≥ 65 years.[1] In the US, the number of influenza-associated deaths might be increasing in part because the number of older persons is increasing.[1,2] In addition, influenza seasons in which influenza A (H3N2) viruses predominate are associated with higher mortality; influenza A (H3N2) viruses predominated in 90% of influenza seasons from 1990–1999 compared with 57% of influenza seasons from 1976–1990.[1]

Vaccinating persons at high risk for complications each year before seasonal increases in influenza virus circulation is the most effective means of reducing the effect of influenza. Vaccination coverage can be increased by administering vaccine to persons during hospitalizations or routine health-care visits before the influenza season, making special visits to physicians' offices or clinics unnecessary. When vaccine and epidemic strains are well-matched, achieving increased vaccination rates among persons living in closed settings (eg, nursing homes and other chronic-care facilities) and among the staff can reduce the risk for outbreaks by inducing herd immunity. Vaccination of health-care workers and other persons in close contact with persons at increased risk for severe influenza illness can also reduce transmission of influenza and subsequent influenza-related complications.[1]

Inactivated influenza vaccines are standardized to contain the hemagglutinins of strains (ie, typically two type A and one type B), representing the influenza viruses likely to circulate in the US in the upcoming winter. The vaccine is made from highly purified, egg-grown viruses that have been made noninfectious (ie, inactivated or "killed").[1]

The effectiveness of influenza vaccine depends primarily on the age and immunocompetence of the vaccine recipient and the degree of similarity between the viruses in the vaccine and those in circulation. The majority of vaccinated children and young adults develop high postvaccination hemagglutination-inhibition antibody titers. These antibody titers are protective against illness caused by strains similar to those in the vaccine.[1]

When the vaccine and circulating viruses are antigenically similar, influenza vaccine prevents illness in approximately 70% to 90% of healthy adults aged < 65 years. Vaccination of healthy adults also has resulted in decreased work absenteeism and decreased use of health-care resources, including the use of antibiotics, when the vaccine and circulating viruses are well-matched.[1]

Older persons and persons with certain chronic diseases might develop lower postvaccination antibody titers than healthy young adults and thus can remain susceptible to influenza-related upper respiratory tract infection. However, among such persons, the vaccine can be effective in preventing secondary complications and reducing the risk for influenza-related hospitalization and death among adults aged ≥ 65 years with and without high risk medical conditions (eg, heart disease and diabetes). Among elderly persons living outside of nursing homes or similar chronic-care facilities, influenza vaccine is 30%-70% effective in preventing hospitalization for pneumonia and influenza. Among elderly persons residing in nursing homes, influenza vaccine is most effective in preventing severe illness, secondary complications, and deaths. Among this population, the vaccine can be 50%-60% effective in preventing hospitalization or pneumonia and 80% effective in preventing death, although the effectiveness in preventing influenza illness often ranges from 30%-40%.[1]

INDICATIONS AND USAGE

Fluzone is indicated only for active immunization against the selected virus strains contained in the vaccine (see **PRECAUTIONS** section).

The optimal time to vaccinate is usually during October through November, because influenza activity in the US generally begins to increase as early as November or December, but has not reached peak levels in the majority of recent seasons until late December. Although vaccine generally becomes available in August or September, in some years, vaccine for the upcoming influenza season might not be available until later in the fall. Administering vaccine before October should generally be avoided in facilities such as nursing homes, because antibody levels can begin to decline within a limited time after vaccination. In addition, health-care providers should also continue to offer vaccine to unvaccinated persons after November and throughout the influenza season even after influenza activity has been documented in the community. In the US, seasonal influenza activity can begin to increase as early as November or December, but influenza activity has not reached peak levels in the majority of recent seasons until late December through early March. Therefore, although the timing of influenza activity can vary by region, vaccine administered after November is likely to be beneficial in the majority of influenza seasons.[1]

Influenza vaccine (subvirion) is strongly recommended for any person aged ≥ 6 months who is at increased risk for complications of influenza. In addition, health-care workers and other persons (including household members) in close contact with persons at high risk should be vaccinated to decrease the risk of transmitting influenza to persons at high risk. Influenza vaccine also can be administered to any person aged ≥ 6 months to reduce the chance of becoming infected with influenza.[1]

Dosage recommendations for the 2003–2004 season are given in Table 1. Guidelines for the use of vaccine among certain patient populations are given below.[1]

Beginning each September, influenza vaccine should be offered, if available, to persons at high risk when they are seen by health-care providers for routine care or are hospitalized. Persons of all ages (including children) with high-risk conditions and persons aged ≥ 50 years who are hospitalized at any time during September – March should be offered and strongly encouraged to receive influenza vaccine before they are discharged.

Persons planning substantial organized vaccination campaigns should consider scheduling these events after mid-October because the availability of vaccine in any location cannot be ensured consistently in the early fall. Scheduling campaigns after mid-October will minimize the need for cancellations because vaccine is unavailable,[1] and will ensure that priority is given to high-risk persons. If regional influenza activity is expected to begin earlier than December, vaccination programs also can be undertaken as early as September. Health-care providers should offer vaccine to unvaccinated persons even after influenza virus activity is documented in a community and should continue to offer vaccine throughout the influenza season.[1] (For information on vaccination of travelers, see ***Travelers*** section.)

The Advisory Committee on Immunization Practices (ACIP) recommends that vaccine providers focus their vaccination efforts in October and earlier primarily on persons aged ≥ 50 years, persons < 50 years at increased risk of influenza-related complications (including children 6-23 months), household contacts of high risk persons (including out-of-home caregivers and household contacts of children 0-23 months), and health-care workers.[1]

Dosage recommendations vary according to age group (Table 1). Among previously unvaccinated children aged < 9 years, who are receiving influenza vaccine for the first time, two doses administered ≥ 1 month apart are recommended for satisfactory antibody responses. If possible, the second dose should be administered before December. Among adults, studies have indicated limited or no improvement in antibody response when a second dose is administered during the same season. Even when the current influenza vaccine contains ≥ 1 antigen administered in previous years, annual vaccination with the current vaccine is necessary because immunity declines during the year after vaccination. Vaccine prepared for a previous influenza season should not be administered to provide protection for the current season.[1]

The intramuscular route is recommended for influenza vaccine. Adults and older children should be vaccinated in the deltoid muscle. A needle length ≥ 1 inch can be considered for these age groups because needles < 1 inch might be of insufficient length to penetrate muscle tissue in certain adults and older children.[1]

Infants and young children should be vaccinated in the anterolateral aspect of the thigh. ACIP recommends a needle length of 7/8 to 1 inch for children < 12 months for intramuscular vaccination into the anterolateral thigh. When injecting into the deltoid muscle among children with adequate deltoid muscle mass, a needle length of 7/8 to 1-1/4 inches is recommended.[1]

SAFETY AND EFFECTIVENESS OF FLUZONE (SUBVIRION) IN INFANTS BELOW THE AGE OF 6 MONTHS HAVE NOT BEEN ESTABLISHED.

TARGET GROUPS FOR VACCINATION

Persons at Increased Risk for Complications

Vaccination is recommended for the following groups of persons who are at increased risk for complications from influenza:[1]

- persons aged ≥ 65 years;
- residents of nursing homes and other chronic-care facilities that house persons of any age who have chronic medical conditions;
- adults and children who have chronic disorders of the pulmonary or cardiovascular systems, including asthma;
- adults and children who have required regular medical follow-up or hospitalization during the preceding year because of chronic metabolic diseases (including diabetes mellitus), renal dysfunction, hemoglobinopathies, or immunosuppression (including immunosuppression caused by medications or by human immunodeficiency virus [HIV]);
- children and adolescents (aged 6 months-18 years) who are receiving long-term aspirin therapy and, therefore, might be at risk for developing Reye syndrome after influenza infection; and
- women who will be in the second or third trimester of pregnancy during the influenza season.

In 2000, approximately 73 million persons in the US fell into ≥ 1 of these target groups, including 35 million persons aged ≥ 65 years; and 12 million adults aged 50-64 years, 18 million adults aged 18-49 years, and 8 million children aged 6 months-17 years with ≥ 1 medical conditions that are associated with an increased risk of influenza-related complications.[1]

Persons Aged 50 to 64 Years

Vaccination is recommended for persons aged 50-64 years because this group has an increased prevalence of persons with high risk conditions. In 2000, approximately 42 million persons in the US were aged 50-64 years, of whom 12 million (29%) had ≥ 1 high-risk medical conditions. Persons aged 50-64 years without high-risk conditions also receive benefit from vaccination in the form of decreased rates of influenza illness, decreased work absenteeism, and decreased need for medical visits and medication, including antibiotics. Further, 50 years is an age when other preventive services begin and when routine assessment of vaccination and other preventive services has been recommended.[1]

Also, persons who smoke tobacco products are at increased risk for influenza-related complications and therefore should receive influenza vaccine.[3-5]

Persons Who Can Transmit Influenza to Those at High Risk:[1]

Persons who are clinically or subclinically infected can transmit influenza virus to persons at high risk for complications from influenza. Decreasing transmission of influenza from caregivers and household contacts to persons at high risk might reduce influenza-related deaths among persons at high risk. Evidence from two studies indicates that vaccination of health-care personnel is associated with decreased deaths among nursing home patients. Vaccination of health-care personnel and others in close contact with persons at high risk, including household contacts, is recommended. The following groups should be vaccinated:[1]

- physicians, nurses, and other personnel in both hospital and outpatient-care settings, including medical emergency response workers (eg, paramedics and emergency medical technicians);
- employees of nursing homes and chronic-care facilities who have contact with patients or residents;
- employees of assisted living and other residences for persons in groups at high risk;
- persons who provide home care to persons in groups at high risk; and
- household contacts (including children) of persons in groups at high risk.

In addition, because children aged 0-23 months are at increased risk for influenza-related hospitalization, vaccination is encouraged for their household contacts and out-of-home caretakers, particularly for contacts of children aged 0-5 months because influenza vaccines have not been approved by the US Food and Drug Administration (FDA) for use among children aged < 6 months.[1]

General Population

Physicians should administer influenza vaccine to any person who wishes to reduce the likelihood of becoming ill with influenza (the vaccine can be administered to children aged ≥ 6 months) depending on vaccine availability. Persons who provide essential community services should be considered for vaccination to minimize disruption of essential activities during influenza outbreaks. Students or other persons in institutional settings (eg, those who reside in dormitories) should be encouraged to receive vaccine to minimize the disruption of routine activities during epidemics.[1]

Healthy Young Children

Studies indicate that rates of hospitalization are higher among young children than older children when influenza viruses are in circulation. The increased rates of hospitalization are comparable with rates for other groups considered at high risk for influenza-related complications. However, the interpretation of these findings has been confounded by co-circulation of respiratory syncytial viruses, which are a cause of serious respiratory viral illness among children and which frequently circulate during the same time as influenza viruses. Two recent studies have attempted to separate the effects of respiratory syncytial viruses and influenza viruses on rates of hospitalization among children who do not have high-risk conditions. Both studies reported that otherwise healthy children aged < 2 years, and possibly children aged 2-4 years, are at increased risk for influenza-related hospitalization compared with older healthy children. Some studies report that trivalent inactivated influenza vaccine decreases the incidence of influenza-associated otitis media among young children by approximately 30%.[1]

Because children aged 6-23 months are at substantially increased risk for influenza-related hospitalizations, ACIP, the American Academy of Pediatrics, and the American Academy of Family Physicians continue to encourage vaccination of all children in this age group when feasible. However, the benefits of a full recommendation to vaccinate all children aged 6-23 months will depend on the identification and implementation of practical and efficient annual influenza vaccination strategies for providers of health care to children. In the interim, the identification of potential strategies for influenza vaccination of children, review of additional data from ongoing studies among children aged 6-23 months receiving influenza vaccine, and efforts to educate parents and providers regarding the impact of influenza and the potential benefits and risks of vaccinating young children will continue. ACIP continues to strongly recommend influenza vaccination of persons aged ≥ 6 months who have high-risk medical conditions.[1]

Pregnant Women

Influenza-associated excess deaths among pregnant women were documented during the pandemics of 1918–1919 and 1957–1958. Case reports and limited studies also indicate that pregnancy can increase the risk for serious medical complications of influenza. An increased risk might result from increases in heart rate, stroke volume, and oxygen consumption; decreases in lung capacity; and changes in immunologic function during pregnancy. A study of the impact of influenza during 17 interpandemic influenza seasons demonstrated that the relative risk for hospitalization for selected cardiorespiratory conditions among pregnant women increased from 1.4 during weeks 14-20 of gestation to 4.7 during weeks 37-42, in comparison with women who were 1-6 months postpartum. Women in their third trimester of pregnancy were hospitalized at a rate (ie, 250/100,000 pregnant women) comparable with that of non-pregnant women who had high-risk medical conditions for whom influenza vaccine has traditionally been recommended. Researchers estimated that an average of 1-2 hospitalizations could be prevented for every 1,000 pregnant women vaccinated.[1]

Because of the increased risk for influenza-related complications, women who will be beyond the first trimester of pregnancy (> 14 weeks of gestation) during the influenza season should be vaccinated. Certain providers prefer to administer influenza vaccine during the second trimester to avoid a coincidental association with spontaneous abortion, which is common in the first trimester, and because exposures to vaccines traditionally have been avoided during the first trimester. Pregnant women who have medical conditions that increase their risk for complications from influenza should be vaccinated before the influenza season, regardless of the stage of pregnancy. A study of influenza vaccination of > 2,000 pregnant women demonstrated no adverse fetal effects associated with influenza vaccine. However, additional data are needed to confirm the safety of vaccination during pregnancy.[1]

The majority of influenza vaccine distributed in the US contains thimerosal, a mercury-containing compound, as a preservative, but influenza vaccine with reduced thimerosal content is available in limited quantities. Thimerosal has been used in US vaccines since the 1930s. No data or evidence exists of any harm caused by the level of mercury exposure that might occur from influenza vaccination. Because pregnant women are at increased risk for influenza-related complications and because a substantial safety margin has been incorporated into the health guidance values for organic mercury exposure, the benefit of influenza vaccine with reduced or standard thimerosal content outweighs the potential risk, if any, for thimerosal.[1]

In view of these and other data that suggest that influenza infection may cause increased morbidity in women during the second and third trimesters of pregnancy, the ACIP recommends that health-care workers who provide care for pregnant women should consider administering influenza vaccine.[1] (Refer to *PREGNANCY CATEGORY C* statement.)

Breastfeeding Mothers
Influenza vaccine does not adversely affect mothers or their infants who are being breastfed. Breastfeeding does not adversely affect immune response and is not a contraindication for vaccination.[1]

Persons Infected with Human Immunodeficiency Virus (HIV)
Limited information is available regarding the frequency and severity of influenza illness or the benefits of influenza vaccination among persons with HIV infection. However, a retrospective study of young and middle-aged women found that the attributable-risk for cardiopulmonary hospitalizations among women with HIV infection was higher during influenza seasons than in the peri-influenza periods. The risk for hospitalization was higher for HIV-infected women than for women with other well-recognized high-risk conditions, including chronic heart and lung diseases. Other reports demonstrate that influenza symptoms might be prolonged and the risk for complications from influenza increased for certain HIV-infected persons.[1]

Influenza vaccination has been demonstrated to produce substantial antibody titers against influenza among vaccinated HIV-infected persons who have minimal acquired immunodeficiency syndrome-related symptoms and high $CD4^+$ T-lymphocyte cell counts. A limited, randomized, placebo-controlled trial determined that influenza vaccine was highly effective in preventing symptomatic, laboratory-confirmed influenza infection among HIV-infected persons with a mean of 400 $CD4^+$ T-lymphocyte cells/mm^3; a limited number of persons with $CD4^+$ T-lymphocyte cell counts of less than 200 were included in that study. Among persons who have advanced HIV disease and low $CD4^+$ T-lymphocyte cell counts, influenza vaccine might not induce protective antibody titers; a second dose of vaccine does not improve the immune response in these persons.[1]

One study determined that HIV RNA levels increased transiently in one HIV-infected patient after influenza infection. Studies have demonstrated a transient (ie, 2-4 week) increase in replication of HIV-1 in the plasma or peripheral blood mononuclear cells of HIV-infected persons after vaccine administration. Other studies using similar laboratory techniques have not documented a substantial increase in replication of HIV. Deterioration of $CD4^+$ T-lymphocyte cell counts or progression of HIV disease have not been demonstrated among HIV-infected persons after influenza vaccination compared with unvaccinated persons. The effect of antiretroviral therapy on increases in HIV RNA levels following either natural influenza infection or influenza vaccination is unknown. Because influenza can result in serious illness and complications and because influenza vaccination can result in the production of protective antibody titers, vaccination will benefit HIV-infected patients, including HIV-infected pregnant women.[1]

Travelers
The risk of exposure to influenza during travel depends on the time of year and destination. In the tropics, influenza can occur throughout the year. In the temperate regions of the Southern Hemisphere, the majority of influenza activity occurs during April–September. In temperate climate zones of the Northern and Southern Hemispheres, travelers also can be exposed to influenza during the summer, especially when traveling as part of large organized tourist groups (eg, on cruise ships) that include persons from areas of the world where influenza viruses are circulating. Persons at high risk for complications of influenza who were not vaccinated with influenza vaccine during the preceding fall or winter should consider receiving influenza vaccine before travel if they plan to:[1]

- travel to the tropics;
- travel with organized tourist groups at any time of year; or
- travel to the Southern Hemisphere during April–September.

No information is available regarding the benefits of revaccinating persons before summer travel who were already vaccinated in the preceding fall. Persons at high risk who received the previous season's vaccine before travel should be revaccinated with the current vaccine in the following fall or winter. Persons aged $\geq$ 50 years and others at high risk might want to consult with their physicians before embarking on travel during the summer to discuss the symptoms and risks for influenza and the advisability of carrying antiviral medications for either prophylaxis or treatment of influenza.[1]

SIMULTANEOUS ADMINISTRATION OF OTHER VACCINES, INCLUDING CHILDHOOD VACCINES
CONCURRENT USE WITH PNEUMOCOCCAL VACCINE. Influenza vaccine has been shown in clinical studies to be acceptable for concurrent use with pneumococcal vaccine using separate syringes at different sites. Although Influenza Virus Vaccine is recommended for annual use, the pneumococcal vaccine is not.[1,6] When indicated, pneumococcal vaccine should be administered to patients who are uncertain regarding their vaccination history. No studies regarding the simultaneous administration of inactivated influenza vaccine and other childhood vaccines have been conducted. Children at high risk for influenza-related complications, including those aged 6-23 months, can receive influenza vaccine at the same time they receive other routine vaccinations.[1]

CONTRAINDICATIONS
INFLUENZA VIRUS IS PROPAGATED IN EGGS FOR THE PREPARATION OF INFLUENZA VIRUS VACCINE. THEREFORE, FLUZONE SHOULD NOT BE ADMINISTERED TO ANYONE WITH A HISTORY OF HYPERSENSITIVITY (ALLERGY), ESPECIALLY ANAPHYLACTIC REACTIONS, TO EGGS OR EGG PRODUCTS. IT IS ALSO A CONTRAINDICATION TO ADMINISTER FLUZONE TO INDIVIDUALS KNOWN TO BE SENSITIVE TO THIMEROSAL. EPINEPHRINE INJECTION (1:1000) MUST BE IMMEDIATELY AVAILABLE SHOULD AN ACUTE ANAPHYLACTIC REACTION OCCUR DUE TO ANY COMPONENT OF FLUZONE.

Fluzone should not be administered to patients with acute respiratory or other active infections or illnesses.

Immunization should be delayed in a patient with an active neurologic disorder, but should be considered when the disease process has been stabilized.

WARNINGS
Fluzone should not be administered to individuals who have a prior history of Guillain-Barré syndrome (GBS).

If Fluzone is administered to immunosuppressed persons, the expected antibody response may not be obtained.

As with any vaccine, vaccination with Fluzone may not protect 100% of susceptible individuals.

PRECAUTIONS
GENERAL
Care is to be taken by the health-care provider for the safe and effective use of this vaccine.

EPINEPHRINE INJECTION (1:1000) MUST BE IMMEDIATELY AVAILABLE SHOULD AN ACUTE ANAPHYLACTIC REACTION OCCUR DUE TO ANY COMPONENT OF THIS VACCINE.

Influenza virus is remarkably capricious in that significant antigenic changes may occur from time to time. *It is known that Influenza Virus Vaccine, as now constituted, is not effective against all possible strains of influenza virus. Protection is limited to those strains of virus from which the vaccine is prepared or to closely related strains.*

During the course of any febrile respiratory illness or other active infection, use of Influenza Virus Vaccine should be delayed.

Since the likelihood of febrile convulsions is greater in children aged 6 months through 35 months, special care should be taken in weighing relative risks and benefits of vaccination.

Prior to an injection of any vaccine, all known precautions should be taken to prevent adverse reactions. This includes a review of the patient's history with respect to possible sensitivity to the vaccine or similar vaccine, to possible sensitivity to dry natural latex rubber, previous immunization history, current health status (see **CONTRAINDICATIONS** and **WARNINGS** sections) and a knowledge of the current literature concerning the use of the vaccine under consideration.

Special care should be taken to prevent injection into a blood vessel.

A separate, sterile syringe and needle or a sterile disposable unit should be used for each patient to prevent transmission of hepatitis or other infectious agents from person to person. Needles should not be recapped and should be disposed of according to biohazard waste guidelines.

Caution: The stopper to the vial contains dry natural latex rubber that may cause allergic reactions.

INFORMATION FOR PATIENT
Patients, parents or guardians should be fully informed by their health-care provider of the benefits and risks of immunization with Influenza Virus Vaccine.

Patients, parents or guardians should be instructed to report any serious adverse reactions to their health-care provider.

Drug Interaction:
Although influenza vaccination can inhibit the clearance of warfarin, theophylline, phenytoin, and aminopyrine therapy, studies have failed to show any adverse clinical effects attributable to these drugs in patients receiving influenza vaccine. [7-13]

If Fluzone is administered to immunosuppressed persons or persons receiving immunosuppressive therapy, the expected antibody response may not be obtained. This includes patients with asymptomatic HIV infection, AIDS or AIDS-Related Complex, severe combined immunodeficiency, hypogammaglobulinemia, or aggammaglobulinemia; altered immune states due to diseases such as leukemia, lymphoma, or generalized malignancy; or an immune system compromised by treatment with corticosteroids, alkylating drugs, antimetabolites or radiation.[14]

PREGNANCY
REPRODUCTIVE STUDIES – PREGNANCY CATEGORY C
Animal reproduction studies have not been conducted with Influenza Virus Vaccine. It is not known whether Influenza Virus Vaccine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Influenza Virus Vaccine should be given to a pregnant woman only if clearly needed. For guidance regarding use in pregnant women, see **INDICATIONS AND USAGE** section.

PEDIATRIC USE
SAFETY AND EFFECTIVENESS OF FLUZONE (SUBVIRION) IN INFANTS BELOW THE AGE OF 6 MONTHS HAVE NOT BEEN ESTABLISHED.

ADVERSE REACTIONS
When educating patients regarding potential side effects, clinicians should emphasize that 1) inactivated influenza vaccine contains noninfectious killed viruses and cannot cause influenza; and 2) coincidental respiratory disease unrelated to influenza vaccine can occur after vaccination.[1]

Local Reactions
In placebo-controlled studies among adults, the most frequent side effect of vaccination is soreness at the vaccination site (affecting 10%-64% of patients) that lasts < 2 days. These local reactions typically are mild and rarely interfere with the person's ability to conduct usual daily activities.[1]

Systemic Reactions
Fever, malaise, myalgia, and other systemic symptoms can occur following vaccination and most often affect persons who have had no prior exposure to the influenza virus antigens in the vaccine (eg, young children).[1,15] These reactions begin 6-12 hours after vaccination and can persist for 1-2 days. Recent placebo-controlled trials demonstrate that among older persons and healthy young adults, administration of split-virus influenza vaccine is not associated with higher rates of systemic symptoms (eg, fever, malaise, myalgia, and headache) when compared with placebo injections.[1]

Immediate – presumably allergic – reactions (eg, hives, angioedema, allergic asthma, and systemic anaphylaxis) rarely occur after influenza vaccination. These reactions probably result from hypersensitivity to certain vaccine components; the majority of reactions probably are caused by residual egg protein. Although current influenza vaccines contain only a limited quantity of egg protein, this protein can induce immediate hypersensitivity reactions among persons who have severe egg allergy. Persons who have had hives or swelling of the lips or tongue or have experienced acute respiratory distress or collapse after eating eggs should consult a physician for appropriate evaluation to help determine if vaccine should be administered. Persons who have documented immunoglobulin E (IgE)-mediated hypersensitivity to eggs, including those who have had occupational asthma or other allergic responses to egg protein, also might be at increased risk for allergic reactions to influenza vaccine, and consultation with a physician should be considered. Protocols have been published for safely administering influenza vaccine to persons with egg allergies.[1,16]

The 1976 swine influenza vaccine was associated with an increased frequency of Guillain-Barré syndrome (GBS).[1,17] Among persons who received the swine influenza vaccine in 1976, the rate of GBS that exceeded the background rate was < 10 cases/1,000,000 persons vaccinated. Evidence for a causal relation of GBS with subsequent vaccines prepared from other influenza viruses is unclear. Obtaining strong epidemiologic evidence for such a possible limited increase in risk is difficult for such a rare condition as GBS, which has an annual incidence of 10-20 cases/1,000,000 adults, and stretches the limits of epidemiologic investigation.[1]

During three of four influenza seasons studied from 1977–1991, the overall relative risk estimates for GBS after influenza vaccination were slightly elevated but were not statistically significant in any of these studies. However, in a study of the 1992–1993 and 1993–1994 seasons, the overall relative risk for GBS was 1.7 (95% confidence interval = 1.0-2.8; p = 0.04) during the 6 weeks after vaccination, representing approximately 1 additional case of GBS/1,000,000 persons vaccinated. The combined number of GBS cases peaked two weeks after vaccination. Thus, investigations to date indicate that there is no substantial increase in GBS associated with influenza vaccines (other than the swine influenza vaccine in 1976), and that, if influenza vaccine does pose a risk, it is probably slightly more than 1 additional case/1,000,000 persons vaccinated.[1]

Even if GBS were a true side effect of vaccination in the years after 1976, the estimated risk for GBS of approximately 1 additional case/1,000,000 persons vaccinated is substantially less than the risk for severe influenza, which could be prevented by vaccination among all age groups, especially persons aged ≥ 65 years and those who have medical indications for influenza vaccination.[1]

The potential benefits of influenza vaccination in preventing serious illness, hospitalization, and death substantially outweigh the possible risks for developing vaccine-associated GBS. The average case-fatality ratio for GBS is 6% and increases with age. No evidence indicates that the case-fatality ratio for GBS differs among vaccinated persons and those not vaccinated.[1]

The incidence of GBS among the general population is low, but persons with a history of GBS have a substantially greater likelihood of subsequently experiencing GBS than persons without such a history. Thus, the likelihood of coincidently experiencing GBS after influenza vaccination is expected to be greater among persons with a history of GBS than among persons with no history of this syndrome. Whether influenza vaccination specifically might increase the risk for recurrence of GBS is not known.[1]

Neurological disorders temporally associated with influenza vaccination such as encephalopathy, optic neuritis/neuropathy,[18,19] partial facial paralysis, and brachial plexus neuropathy have been reported. However, no cause and effect has been established.[20,21] Almost all persons affected were adults, and the described clinical reactions began as soon as a few hours and as late as 2 weeks after vaccination. Full recovery was almost always reported.[17,22,23]

Microscopic polyangitis (vasculitis) has been reported temporally associated with influenza vaccination. However, no cause and effect has been established.[24]

Reporting of Adverse Events
Reporting by patients, parents, or guardians of all adverse events after vaccine administration should be encouraged. Adverse events following immunization with vaccine should be reported by health-care providers to the US Department of Health and Human Services (DHHS) Vaccine Adverse Event Reporting System (VAERS). Reporting forms and information about reporting requirements or completion of the form can be obtained from VAERS through a toll-free number 1-800-822-7967.[25]

The health-care providers also should report these events to the Pharmacovigilance Department, Aventis Pasteur Inc., Discovery Drive, Swiftwater, PA 18370 or call 1-800-822-2463.

DOSAGE AND ADMINISTRATION
Parenteral drug products should be inspected visually for particulate matter and/or discoloration prior to administration whenever solution and container permit. If either of these conditions exist, the vaccine should not be administered.

To help avoid HIV (AIDS), HBV (Hepatitis) and other infectious diseases due to accidental needlesticks, contaminated needles should not be recapped or removed, unless there is no alternative or such action is required by a specific medical procedure.

The vial should be shaken well before withdrawing each 0.5 mL dose.

The prefilled syringe should be shaken well before administering each dose. The 0.25 mL prefilled syringe is preferred for use when 0.25 mL is indicated for children. An alternate immunization method for children when one dose of 0.25 mL is indicated and the 0.5 mL prefilled syringe is being used, is to push the plunger of the 0.5 mL prefilled syringe exactly to the edge of the mark so that half of the volume is discarded. The remaining volume should then be injected.

Do NOT inject intravenously.

Injections of Influenza Virus Vaccine should be administered intramuscularly, preferably in the region of the deltoid muscle, in adults and older children. A needle length of ≥ 1 inch is preferred for these age groups because needles < 1 inch might be of insufficient length to penetrate muscle tissue in certain adults and older children. The preferred site for infants and young children is the anterolateral aspect of the thigh.[1] Before injection, the skin over the site to be injected should be cleansed with a suitable germicide. After insertion of the needle, aspirate to assure that the needle has not entered a blood vessel.

Influenza vaccine should be offered beginning in September (see **INDICATIONS AND USAGE** section).

Children < 9 years who have not previously been vaccinated should receive two doses of vaccine ≥ 1 month apart to maximize the likelihood of a satisfactory antibody response to all three vaccine antigens. If possible, the second dose should be administered before December.[1]

Fluzone (Subvirion) is to be used for persons 6 months of age and older. Fluzone (Subvirion) is NOT approved for infants under 6 months of age. The dosage is as follows:

TABLE 1[1] **Influenza Vaccine Dosage by Age Group 2003–2004 Season**

Age Group	Dosage	No. of Doses	Route§
6 – 35 months	0.25 mL	1 or 2*	Intramuscular
3 – 8 years	0.50 mL	1 or 2*	Intramuscular
≥ 9 years	0.50 mL	1	Intramuscular

§ For adults and older children, the recommended site of vaccination is the deltoid muscle. The preferred site for infants and young children is the anterolateral aspect of the thigh.

* Two doses administered at least one month apart are recommended for children < 9 years who are receiving influenza vaccine for the first time.

HOW SUPPLIED

Luer-Lok™ syringe, without needle, 0.25 mL (10 per package) (contains NO preservative). Shake syringe well before administering. Product No. 49281-371-25 – CPT® Code: 90655

Luer-Lok™ syringe, without needle, 0.5 mL (10 per package) (contains preservative). Shake syringe well before administering. Product No. 49281-372-11 – CPT® Code: 90658, 0.5 mL, age 3 years and older; CPT® Code: 90657, 0.25 mL, age 6 to 35 months

Vial, 5 mL, for administration with needle and syringe (contains preservative). Shake vial well before withdrawing each dose. Product No. 49281-372-15 – CPT® Code: 90658, 0.5 mL, age 3 years and older; CPT® Code: 90657, 0.25 mL, age 6 to 35 months

Luer-Lok™ is a trademark of Becton Dickinson and Company.

CPT is a registered trademark of the American Medical Association.

STORAGE

Store between 2° – 8°C (35° – 46°F). Potency is destroyed by freezing. **DO NOT USE FLUZONE IF IT HAS BEEN FROZEN.**

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