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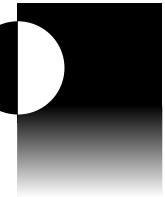
Influenza Virus Vaccine USP

Trivalent Types A and B
(Zonal Purified, Subvirion)

2001 – 2002 Formula

For 6 Months and Older

Fluzone®

SPECIAL NOTICE: FOR USE IN IMMUNIZATION BY OR UNDER THE DIRECTION OF A PHYSICIAN.

Caution: Federal (USA) law prohibits dispensing without prescription.

DESCRIPTION

Fluzone®, Influenza Virus Vaccine USP, (Zonal Purified, Subvirion) for intramuscular use, is a sterile suspension prepared from influenza viruses propagated in chicken embryos. 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 Polyethylene Glycol p-Isooctylphenyl Ether (Triton® X-100 – A registered trademark of Rohm and Haas, Co.) producing a “split-antigen.” The split-antigen 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 2001-2002 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/Victoria/504/2000 (a B/Sichuan/379/99-like strain).¹ Each dose contains the preservative thimerosal [(mercury derivative), 25 µg mercury/dose] and gelatin 0.05% added as a stabilizer. 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 occur during the winter months nearly every year and are responsible for an average of approximately 20,000 deaths per year in the United States (US). Influenza viruses also can cause global epidemics of disease, known as pandemics, during which rates of illness and death from influenza-related complications can increase dramatically. Influenza viruses cause disease in all age groups. Rates of infection are highest among children, but rates of serious illness and death are highest among persons greater than or equal to 65 years of age and persons of any age who have medical conditions that place them at high risk for complications from influenza.¹

Influenza vaccine is the primary method for preventing influenza and its more severe complications. The primary target group for influenza vaccination includes a) persons who are at high risk for serious complications from influenza (eg, persons aged greater than or equal to 65 years and persons of any age with certain chronic medical conditions); b) the group aged 50 to 64 years because this group has an elevated prevalence of certain chronic medical conditions; and c) 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 can transmit influenza infections to these 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 greater than or equal to 65 years of age, influenza vaccination levels increased from 33% in 1989 to 63% in 1997. Although influenza vaccination coverage increased in black, Hispanic, and white populations, vaccination levels among blacks and Hispanics continue to lag behind those among whites.¹

Increasing vaccination coverage among persons at high risk less than 65 years of age now is the highest priority for expanding influenza vaccine use.¹

Vaccination of health-care workers has been associated with reduced work absenteeism, and decreased deaths among nursing home patients. Efforts should be made to educate health-care workers about 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 (i.e., 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 the severity of disease if infection occurs. However, antibody against one influenza virus type or subtype confers little or no protection against another virus type or subtype. Furthermore, antibody to one antigenic variant of influenza virus might not protect against a new antigenic variant of the same type or subtype. The frequent development of antigenic variants through antigenic drift is the virologic basis for seasonal epidemics and the reason for the incorporation of one or more 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 one to four days with an average of two days. Persons can be infectious starting the day before symptoms begin through approximately five days after illness onset; children can be infectious for a longer period. Uncomplicated influenza illness is characterized by the abrupt onset of constitutional and respiratory signs and symptoms (e.g., fever, myalgia, headache, severe malaise, nonproductive cough, sore throat, and rhinitis). Illness typically resolves after several days in most persons, although cough and malaise can persist for two or more weeks. In some persons, influenza can exacerbate underlying medical conditions (e.g., pulmonary or cardiac disease) or lead to secondary bacterial pneumonia or primary influenza viral pneumonia.¹

The risks for complications, hospitalization, and deaths from influenza are higher among persons greater than or equal to 65 years of age, very young children, and persons of any age with some underlying health conditions than among healthy older children and younger adults. Estimated rates of influenza-associated hospitalizations have varied substantially by age group in studies conducted during different influenza epidemics:¹

- Among children 0 to 4 years of age, rates have ranged from approximately 500 per 100,000 population for those with high-risk conditions to 100 per 100,000 population for those without high-risk conditions.¹ Among children without high-risk conditions, rates differ substantially within the 0- to 4-year age group: babies less than 6 months of age have the highest hospitalization rate at approximately 1,040 per 100,000 population, and children 2 to 4 years of age are hospitalized at a rate of approximately 8 to 136 per 100,000 population.¹
- Among children 5 to 14 years of age, rates have ranged from approximately 200 per 100,000 population for those with high-risk conditions to 20 to 40 per 100,000 population for those without high-risk conditions.¹
- Among persons 15 to 44 years of age, rates have ranged from approximately 40 to 60 per 100,000 population for those with high-risk conditions to approximately 20 to 30 per 100,000 population for those without high-risk conditions.¹
- Among persons 45 to 64 years of age, rates have ranged from approximately 80 to 400 per 100,000 population for those with high-risk medical conditions to approximately 20 to 40 per 100,000 population for those without high-risk conditions.¹
- Among persons greater than or equal to 65 years of age, rates have ranged from approximately 200 to greater than 1,000 per 100,000 population.¹

During influenza epidemics from 1969-1970 through 1993-1994, the estimated overall number of influenza-associated hospitalizations in the US has ranged from approximately 16,000 to greater than 220,000 per epidemic. An analysis of national hospital discharge data indicates that an average of approximately 114,000 excess hospitalizations per year are related to influenza. 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

During influenza epidemics, deaths can increase from influenza and pneumonia as well as from exacerbations of cardiopulmonary conditions and other chronic diseases. In studies of influenza epidemics occurring from 1972-1973 through 1994-1995, excess deaths (i.e., the number of influenza-related deaths above a projected baseline of expected deaths) occurred during 19 of 23 influenza epidemics. During those 19 influenza seasons, estimated rates of influenza-associated deaths ranged from approximately 30 to greater than 150 deaths per 100,000 persons greater than or equal to 65 years of age. These older adults currently account for more than 90% of the deaths attributed to pneumonia and influenza. From 1972-1973 through 1994-1995, more than 20,000 influenza-associated deaths were estimated to occur during each of 11 different US epidemics, and more than 40,000 influenza-associated deaths were estimated for each of six of these 11 epidemics. In the US, pneumonia and influenza deaths might be increasing in part because the number of elderly persons is increasing.¹

Vaccinating persons at high risk for complications before the influenza season each year is the most effective means of reducing the impact 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 of virus are well matched, achieving high vaccination rates among persons living in closed settings (e.g., 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 in high-risk groups also can help reduce transmission of influenza and subsequent influenza-related complications.¹

Influenza vaccine contains three virus strains (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 (inactivated).¹

Most 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. 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. When the antigenic match between vaccine and circulating viruses is close, influenza vaccine prevents illness in approximately 70% to 90% of healthy persons younger than 65 years of age. 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. Other studies suggest that the use of trivalent inactivated influenza vaccine decreases the incidence of influenza-associated otitis media and the use of antibiotics among children.¹

Elderly 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 elderly persons living outside of nursing homes or similar chronic-care facilities, influenza vaccine is 30% to 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. In this population, the vaccine can be 50% to 60% effective in preventing hospitalization or pneumonia and 80% effective in preventing death, even though the effectiveness in preventing influenza illness often ranges from 30% to 40%.¹

INDICATIONS AND USAGE

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

The optimal time to vaccinate persons in high-risk groups is usually from the beginning of October through November, because influenza activity in the US generally peaks between late December and early March. Although vaccine generally becomes available in August or September, in some years, vaccine for the upcoming influenza season might not be available in some locations 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 few months 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 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 most influenza seasons.¹

Influenza vaccine (subvirion) is strongly recommended for any person greater than or equal to 6 months of age who – because of age or underlying medical condition – is at increased risk for complications of influenza. In addition, health-care workers and other individuals (including household members) in close contact with persons in high-risk groups should be vaccinated to decrease the risk of transmitting influenza to persons at high risk. Influenza vaccine also can be administered to any person greater than or equal to 6 months of age to reduce the chance of becoming infected with influenza.¹

Dosage recommendations for the 2001-2002 season are given in Table 1. Guidelines for the use of vaccine among certain patient populations are given below.¹

REMAINING 2000-2001 VACCINE SHOULD NOT BE USED TO PROVIDE PROTECTION FOR THE 2001-2002 INFLUENZA SEASON.¹

Beginning each September, influenza vaccine should be offered to persons at high risk when they are seen by health-care providers for routine care or are hospitalized. Persons planning substantial organized vaccination campaigns might consider scheduling these events after mid-October. Although influenza vaccine generally becomes available by September, 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.)

Dosage recommendations vary according to age group (Table 1). Among previously unvaccinated children younger than 9 years of age, two doses administered at least one month apart are recommended for satisfactory antibody responses. If possible, the second dose should be administered before December. Among adults, studies have indicated little or no improvement in antibody response when a second dose is administered during the same season. Even when the current influenza vaccine contains one or more of the antigens administered in previous years, annual vaccination with the current vaccine is necessary because immunity declines during the year following vaccination. Vaccine prepared for a previous influenza season should not be administered to provide protection for the current season.¹

During recent decades, data on influenza vaccine immunogenicity and side effects have been obtained for intramuscularly administered vaccine. Because recent influenza vaccines have not been adequately evaluated when administered by other routes, the intramuscular route is recommended. Adults and older children should be vaccinated in the deltoid muscle; a needle length greater than or equal to 1 inch can be considered for these age groups. Infants and young children should be vaccinated in the anterolateral aspect of the thigh.¹

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

TARGET GROUPS FOR VACCINATION

Groups 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 greater than or equal to 65 years of age;
- 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]);
- infants, children and teenagers (6 months to 18 years of age) 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.

Approximately 35 million persons in the US are aged greater than or equal to 65 years; an additional 10 to 13 million adults aged 50 to 64 years, 15 to 18 million adults aged 18 to 49 years, and 8 million children aged 6 months to 17 years have one or more 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 to 64 years because this group has an increased prevalence of persons with high-risk conditions. Approximately 41 million persons in the US are aged 50 to 64 years, and 10 to 13 million (24% – 32%) have one or more high-risk medical conditions. Persons aged 50 to 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.²⁻⁴

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 care-givers to persons at high risk might reduce influenza-related deaths among persons at high risk. Evidence from two studies suggest that vaccination of health-care workers is associated with decreased deaths among nursing home patients. Vaccination of health-care workers and others in close contact with persons at high risk is recommended. The following groups should be vaccinated:¹

- physicians, nurses, and other personnel in both hospital and outpatient-care settings, including emergency response workers;
- 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 high-risk groups;
- persons who provide home care to persons in high-risk groups; and
- household members (including children) of persons in high-risk groups.

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 as young as 6 months of age). 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 (e.g., those who reside in dormitories) should be encouraged to receive vaccine to minimize the disruption of routine activities during epidemics.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 suggest that pregnancy can increase the risk for serious medical complications of influenza as a result of increases in heart rate, stroke volume, and oxygen consumption; decreases in lung capacity; and changes in immunologic function. 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 to 20 of gestation to 4.7 during weeks 37 to 42 in comparison with women who were 1 to 6 months postpartum. The risk during the third trimester was comparable to the risk for non-pregnant women with high-risk medical conditions for whom influenza vaccine has traditionally been recommended. It was estimated that immunizing 1,000 women who would be in their third trimester during influenza season would prevent one hospitalization.¹

Because currently available influenza vaccine is an inactivated vaccine, experts consider influenza vaccination safe during any stage of pregnancy. A study of influenza vaccination of greater than 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. Some experts 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.¹

Influenza vaccine distributed in the US contains thimerosal, a mercury-containing compound, as a preservative. This preservative 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 outweighs the potential risks 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 affect the safety of mothers who are breastfeeding or their infants. 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 recent 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 of hospitalization for HIV-infected women was higher than the risk for women with other well-recognized high-risk conditions for influenza complications, including chronic heart and lung diseases. Other reports suggest that influenza symptoms might be prolonged and the risk for complications from influenza increased for some HIV-infected persons.¹

Influenza vaccination has been shown to produce substantial antibody titers against influenza in vaccinated HIV-infected persons who have minimal acquired immunodeficiency syndrome-related symptoms and high CD4+ T-lymphocyte cell counts. A small, randomized, placebo-controlled trial found 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/mm³; few persons with CD4+ T-lymphocyte cell counts of less than 200 were included in this study. In patients 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 found that HIV RNA levels increased transiently in one HIV-infected patient after influenza infection. Some studies have demonstrated a transient (i.e., 2- to 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 following influenza vaccination. The effect of antiretroviral therapy on potential 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 many 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, most influenza activity occurs from April through 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 that includes 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 large organized tourist groups at any time of year; or
- travel to the Southern Hemisphere from April through 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 greater than or equal to 50 years of age and others at high risk might wish to consult with their physicians before embarking on travel during the summer to discuss the symptoms and risks of 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. Fluzone 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 should only be given once.^{3,5} Children at high risk for influenza-related complications 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 definitely 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 against 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 6 months through 35 months of age, 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 side 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 and the syringe needle cover contain 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.⁵⁻¹²

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 agammaglobulinemia; 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.^{1,3}

PREGNANCY

REPRODUCTIVE STUDIES – PREGNANCY CATEGORY C

Animal reproduction studies have not been conducted with Influenza Virus Vaccine USP Trivalent, Types A and B. 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 (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 about potential side effects, clinicians should emphasize that a) inactivated influenza vaccine contains noninfectious killed viruses and cannot cause influenza; and b) coincidental respiratory disease unrelated to influenza vaccine can occur after vaccination.¹

Local Reactions

In placebo-controlled blinded studies, the most frequent side effect of vaccination is soreness at the vaccination site (affecting 10% to 64% of patients) that lasts up to 2 days. These local reactions generally 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 exposure to the influenza virus antigens in the vaccine (e.g., young children).^{1,14} These reactions begin 6 to 12 hours after vaccination and can persist for 1 to 2 days. Recent placebo-controlled trials suggest that among elderly persons and healthy young adults, administration of split-virus vaccine is not associated with higher rates of systemic symptoms (e.g., fever, malaise, myalgia, and headache) when compared with placebo injections.¹

Immediate – presumably allergic – reactions (e.g., hives, angioedema, allergic asthma, and systemic anaphylaxis) rarely occur after influenza vaccination. These reactions probably result from hypersensitivity to some vaccine component; most reactions likely are caused by residual egg protein. Although current influenza vaccines contain only a small quantity of egg protein, this protein can induce immediate hypersensitivity reactions among persons who have severe egg allergy. Persons who have developed hives, have had 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.^{1,15}

The 1976 swine influenza vaccine was associated with an increased frequency of Guillain-Barré syndrome (GBS).^{1,16} Among persons who received the swine influenza vaccine in 1976, the rate of GBS that exceeded the background rate was slightly less than 10 cases per million persons vaccinated. Evidence for a causal relationship of GBS with subsequent vaccines prepared from other influenza viruses is less clear. Obtaining strong epidemiologic evidence for a possible small increase in risk is difficult for a rare condition such as GBS, which has an annual incidence of only 10 to 20 cases per million adults, and stretches the limits of epidemiologic investigation.¹

During three of four influenza seasons studied from 1977 through 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 six weeks following vaccination, representing an excess of slightly more than one additional case of GBS per million persons vaccinated; the combined number of GBS cases peaked two weeks after vaccination. Thus, investigations to date suggest that there is no large 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 quite small – slightly more than one additional case per million persons vaccinated.¹

Even if GBS were a true side effect of vaccination in the years after 1976, the estimated risk for GBS of slightly more than one additional case per million persons vaccinated is substantially less than the risk for severe influenza, which could be prevented by vaccination in all age groups, especially persons greater than or equal to 65 years of age and those who have medical indications for influenza vaccination. During different epidemics occurring from 1972 through 1981, estimated rates of influenza-associated hospitalization have ranged from approximately 200 to 300 hospitalizations per million population for previously healthy persons 5 to 44 years of age and from 2,000 to greater than 10,000 hospitalizations per million population for persons greater than or equal to 65 years of age. During epidemics from 1972-1973 through 1994-1995, estimated rates of influenza-associated deaths have ranged from approximately 300 to greater than 1,500 per million persons greater than or equal to 65 years of age, who account for more than 90% of all influenza-associated deaths. The potential benefits of influenza vaccination in preventing serious illness, hospitalization, and death greatly outweigh the possible risks for developing vaccine-associated GBS. The average case-fatality ratio for GBS is 6% and increases with age. However, no evidence indicates that the case-fatality ratio for GBS differs among vaccinated persons and those not vaccinated.¹

The incidence of GBS in the general population is very low, but persons with a history of GBS have a substantially greater likelihood of subsequently developing GBS than persons without such a history. Thus, the likelihood of coincidentally developing 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,^{1,7,18} partial facial paralysis, and brachial plexus neuropathy have been reported. However, no cause and effect has been established.^{1,9,20} 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.^{1,4,21,22}

Microscopic polyangiitis (vasculitis) has been reported temporally associated with influenza vaccination. However, no cause and effect has been established.^{2,3}

Reporting of Adverse Events

Reporting by patients, parents or guardians of all adverse events occurring after vaccine administration should be encouraged. Adverse events following immunization with vaccine should be reported by the health-care provider to the US Department of Health and Human Services (DHHS) Vaccine Adverse Event Reporting Systems (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.^{2,4}

The health-care provider also should report these events to the Director of Scientific and Medical Affairs, 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.

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

The prefilled syringe should be shaken well before administering each 0.5 mL dose. For children, when one dose of 0.25 mL is indicated, push the plunger exactly to the edge of the mark so that half of the volume is eliminated. The remaining volume should 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 greater than or equal to one inch is preferred for these age groups because needles less than one inch might be of insufficient length to penetrate muscle tissue in certain adults and older children.¹ The preferred site for infants and young children is the anterolateral aspect of the thigh. 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 less than 9 years of age who have not previously been vaccinated should receive two doses of vaccine at least one month apart to maximize the likelihood of a satisfactory antibody response to all three vaccine antigens. The second dose should be administered before December, if possible.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 1¹ **Influenza Vaccine Dosage by Age Group**
2001 – 2002 Season

Age Group	Vaccine†	Dosage	No. of Doses	Route§
6 – 35 months	Split virus only	0.25 mL	1 or 2*	Intramuscular
3 – 8 years	Split virus only	0.50 mL	1 or 2*	Intramuscular
9 – 12 years	Split virus only	0.50 mL	1	Intramuscular
> 12 years	Whole or split virus**	0.50 mL	1	Intramuscular

† Because of decreased potential for causing febrile reactions, only split-virus (subvirion) vaccines should be used for children. Immunogenicity and side effects of split- and whole-virus vaccines are similar among adults when vaccines are administered at the recommended dosage.

§ 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 less than 9 years of age who are receiving influenza vaccine for the first time.

** No whole virus vaccine will be distributed in the US during the 2001-2002 influenza season.

HOW SUPPLIED

Syringe with 1" needle, 0.5 mL. (Shake syringe well before administering.) For children, when one dose of 0.25 mL is indicated, push the plunger exactly to the edge of the mark so that half of the volume is eliminated. The remaining volume should be injected. – Product No. 49281-368-11

Vial, 5 mL, for administration with needle and syringe (Shake vial well before withdrawing each dose.) – Product No. 49281-368-15

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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