

Influenza Season: 2008-2009

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Introduction: According to the Centers for Disease Control and Prevention (CDC), the influenza vaccine is the most important step in protecting against influenza each season.¹ More than 130 million doses of influenza vaccine will be manufactured in the United States for the 2008-2009 influenza season.² Influenza causes a considerable amount of morbidity and mortality each year and affects people of all ages. For the past two decades, an average of 36,000 deaths occurred annually in the United States; 90% of these were among the elderly.³ Individuals at highest risk of developing serious complications include adults ≥ 65 years of age and children < 2 years of age, and individuals with certain medical conditions, such as congestive heart failure, diabetes mellitus, and immunosuppressed individuals.¹ Recommendations from the Advisory Committee on Immunization Practices (ACIP) are published each year outlining the individuals who should receive an influenza vaccine.² These recommendations are listed in Table 1.

Persons at Increased Risk for Medical Complications: Vaccination to prevent influenza is particularly important for individuals who are at increased risk for severe complications from influenza or at higher risk for influenza-associated clinic, emergency department, or hospital visits (See Table 2).² When vaccine

supply is limited, vaccination efforts should focus on delivering vaccination to these individuals.

Influenza Virus: Annual epidemics of influenza usually occur from late fall to early spring.^{2,3} The virus is highly contagious and is spread by coughing, sneezing, or nasal secretions. Influenza generally comes on suddenly and symptoms include muscle aches, fatigue, fever, chills, headache, cough, and sore throat. Complications from influenza include pneumonia, dehydration, and worsening of chronic medical conditions, such as congestive heart failure, asthma, or diabetes mellitus. In children, influenza can cause high fever, diarrhea, seizures and can lead to sinus problems and ear infections. The influenza virus is hard to distinguish from other respiratory illnesses based solely on symptoms. A rapid diagnostic influenza test, most often involving a nasopharyngeal swab, may be ordered by a physician to confirm the presence of the virus.⁴

Influenza virus can be classified into two broad subtypes, influenza A and B.^{2,3} Both influenza A and B viruses are further classified into groups based on cell surface antigens. Influenza A is categorized into subtypes on the basis of two cell surface antigens: hemagglutinin (H) and

neuroaminidase (N). Each of these antigens is further divided into subtypes (e.g., H1, H2, or N2). The influenza B viruses are separated into two distinct genetic lineages, Yamagata and Victoria, but are not categorized into subtypes. New viral strains of influenza result from changes in the cell surface antigens (i.e., antigenic drift) caused by mutations that occur during viral replication. Influenza B viruses undergo antigenic drift less rapidly than influenza A viruses. Due to change in the types of viruses circulating each year, some of the components of the influenza vaccine must be changed annually.

Even though there are many strains of the influenza virus, not all strains will cause complications in a given influenza season.^{2,3} Each year the viral components of the influenza vaccine change based on projected virulent strands determined by the World Health Organization (WHO) and the U.S. and Canadian Public Health Services for the Northern Hemisphere. Strains are selected in the spring and released by manufacturers in the fall for the influenza season. The 2008-2009 influenza vaccine contains the following subtypes of influenza A and B, which are named for the location, sequence number, and year of their isolation, respectively: A/Brisbane/59/2007 (H1N1)-like, A/Brisbane/10/2007 (H3N2)-like, and B/Florida/4/2006-like antigens.

Table 1: Influenza Vaccination Recommendations for the 2008-2009 Influenza Season²

Children and Adolescents
Persons aged 6 months-18 years
Adults
Any adult who wants to reduce the risk of becoming ill with influenza or transmitting it to others
Persons aged ≥ 50 years
Women who will be pregnant during influenza season
Persons with chronic pulmonary (including asthma), cardiovascular (except hypertension), renal, hepatic, hematological or metabolic disorders (including diabetes mellitus)
Persons who have immunosuppression that is drug-induced or caused by human immunodeficiency virus (HIV)
Persons who have a condition that can compromise respiratory function or handling of respiratory secretions, or that can increase risk for aspiration (e.g., cognitive dysfunction, spinal cord injuries, seizure disorders, or other neuromuscular disorders)
Residents of nursing homes and other chronic care facilities
Health care personnel
Household contacts and caregivers of children aged < 5 years and adults aged > 50 years, with particular emphasis on vaccinating contacts of children aged < 6 months
Household contacts and caregivers of persons with medical conditions that put them at higher risk for severe complications from influenza

Table 2: Individuals at High Risk for Severe Complications²

All children aged 6 months-4 years
All persons aged ≥ 50 years
Children and adolescents (aged 6 months-18 years) who are receiving long-term aspirin therapy and who might be at risk for experiencing Reye's syndrome after influenza virus infection
Women who will be pregnant during influenza season
Adults and children who have chronic pulmonary (including asthma), cardiovascular (except hypertension), renal, hepatic, hematological or metabolic disorders (including diabetes mellitus)
Adults and children who have immunosuppression (including immunosuppression caused by medications or HIV)
Adults and children who have any condition that can compromise respiratory function or the handling of respiratory secretions that can increase the risk for aspiration (e.g., cognitive dysfunction, spinal cord injuries, seizure disorders, or other neuromuscular disorders)
Residents of nursing homes and other chronic care facilities

Types of Influenza Vaccine: The influenza vaccine was first introduced in the U.S. in 1945 as an injectable vaccine.³ Until recently, all available influenza vaccines were trivalent inactivated, or killed virus vaccines (TIV), commonly referred to as the "flu shot." Despite common misconception, trivalent inactivated vaccines cannot cause influenza because they contain killed viruses. Today in the U.S., only subvirion (split) and purified surface antigen (subunit) preparations of TIV are available. Prior to 2001, inactivated vaccines were also available in whole-virus preparations, but whole-virus preparations caused more fever and reactions at the injection site. The injectable form of the influenza vaccine is prepared by a number of pharmaceutical companies and is available in a variety of forms, including single-dose prefilled syringes and multidose vials; refer to Table 3.⁵

Table 3: Commercially Available Influenza Vaccines

Vaccine	Formulations	Thimerosal*	Age Indication
Inactivated (TIV)			
Afluria® (CSL Biotherapies)	0.5 mL syringe 5 mL multidose vial	None 24.5 mcg/0.5 mL	≥ 18 years ≥ 18 years
Fluarix® (GlaxoSmithKline)	0.5 mL syringe	≤ 1 mcg	≥ 18 years
Fluvirin® (Novartis)	0.5 mL syringe 5 mL multidose vial	< 1 mcg 24.5 mcg/0.5 mL	≥ 4 years ≥ 4 years
Fluzone® (Sanofi Pasteur)	0.25 mL syringe	None	6-35 months
	0.5 mL syringe	None	≥ 3 years
	0.5 mL vial	None	≥ 3 years
	5 mL multidose vial	25 mcg/0.5 mL	≥ 6 months
FluLaval® (GlaxoSmithKline)	5 mL multidose vial	25 mcg/0.5 mL	≥ 18 years
Live attenuated (LAIV)			
FluMist® (MedImmune)	0.2 mL sprayer	None	2-49 years

*Thimerosal is a mercury containing, antibacterial preservative

Table adapted from The Medical Letter on Drugs and Therapeutics⁵

The second type of influenza vaccine is a live, attenuated or weakened (LAIV), trivalent vaccine administered intranasally.^{2-3,6} This route of administration is unique and differs from all other vaccines currently available (See Table 3). The LAIV was introduced in June of 2003 and licensed as FluMist®. Type A and B strains of influenza virus contained in LAIV multiply in the nasal passages but not in the lower respiratory tract and can potentially cause mild signs or symptoms including runny nose, nasal congestion, fever, or sore throat. FluMist® is only approved by the Food and Drug Administration (FDA) for use in persons aged 2-49 years. In addition, the FDA has indicated that the safety of FluMist® has not been established in persons with underlying medical conditions that confer a higher risk for influenza complications (See Table 2). Transmission of influenza from a recently vaccinated person using LAIV is of potential concern, particularly for immunocompromised individuals. Therefore, it is recommended that health care workers and hospital visitors who receive LAIV avoid contact with a severely immunocompromised patient for 7 days after vaccination. Because the effectiveness and safety of LAIV is unknown in many patient populations, the ACIP has recommended that the following groups **not** receive this preparation of the influenza vaccine: children aged 2-4 years with a history of asthma or wheezing within the preceding 12 months, children or adolescents receiving aspirin or other salicylates (due to an association with Reye's syndrome and influenza virus), and persons with underlying medical conditions that require routine influenza vaccination (e.g., asthma, reactive airway disease, chronic pulmonary or cardiovascular disorders, diabetes mellitus, renal dysfunction, known or suspected immunodeficiency disease or immunosuppressed states, and pregnant women).

Pregnant Patients: The ACIP recommends women who are pregnant or will be pregnant during the influenza season be vaccinated with an injectable inactivated vaccine (See Table 3). FluMist® (LAIV) is only FDA-approved for use in healthy persons aged 2-49 years *who are not pregnant*.³ However, pregnant women do not need to avoid contact with persons recently vaccinated with LAIV. Breastfeeding is not a contraindication for influenza vaccination. Therefore, breastfeeding mothers are included in the recommendations for TIV or LAIV unless contraindicated because of other medical conditions.

Cleveland Clinic Health System (CCHS) Employee Vaccination: Fluzone® (Sanofi Pasteur) will be administered at influenza clinics throughout the Cleveland Clinic Health System for the 2008-2009 influenza season. Fluzone® is indicated for use in persons aged ≥ 6 months of age against influenza disease.⁷ Fluzone® is a latex-free product. Preservative-free preparations are available from the manufacturer but are not routinely ordered for employee influenza clinics throughout CCHS. There are concerns surrounding the administration of a live, attenuated virus in immunocompromised individuals (i.e., shedding of live viral particles with potential infection of those susceptible). *Therefore, the live, attenuated virus vaccine, FluMist®, may only be administered to family members of employees given there are no contraindications for its use.*

Persons Who Should NOT Receive Influenza Vaccine: Administration of Fluzone® is contraindicated in individuals with severe allergic reaction to eggs or egg proteins because it is prepared from influenza virus propagated in embryonated chicken eggs.^{2,7} Furthermore, hypersensitivity to any component of the influenza vaccine or a previous life-threatening reaction to the influenza vaccine is a contraindication to vaccination. Individuals with moderate to severe acute illness with fever should not be vaccinated until their symptoms have resolved.

Persons Who Should NOT Receive Influenza Vaccine (continued): Minor illnesses, however, are not a contraindication for influenza vaccination. Finally, if Guillain-Barré syndrome (GBS) has occurred within 6 weeks of previous influenza vaccination, the decision to give Fluzone[®] should be based on careful consideration of the potential benefits and risks.⁷

Dosage and Administration: Dosage recommendations and schedules vary according to age group, which are outlined in Table 4.⁷ All children aged 6 months-8 years who have not been vaccinated previously at any time with at least one dose of the influenza vaccine should receive two doses of age-appropriate vaccine in the same season at least one month apart from each other (See Table 4). If they only receive one dose of the influenza vaccine, two doses are required the following influenza season. Adults and older children should be vaccinated in the deltoid muscle. Infants and young children should be vaccinated in the anterolateral aspect of the thigh.

Table 4: Dosage and Administration Recommendations for Fluzone^{®7}

<u>Age</u>	<u>Dose for Intramuscular Injection</u>	
6-35 months	Previously unvaccinated	Two 0.25 ml doses, one on day 1, followed by another 0.25 mL dose at least one month later
	Previously vaccinated	One 0.25 mL dose
36 months-8 years	Previously unvaccinated	Two 0.5 mL doses, one on day 1, followed by another 0.5 mL dose at least one month later
	Previously vaccinated	One 0.5 mL dose
≥ 9 years and Adults	Previously unvaccinated or vaccinated	One 0.5 mL dose

Previously vaccinated = patient received two doses within the same influenza season

Storage and Stability: Fluzone[®] should be stored at 35°F-46°F (2°C-8°C) and should not be frozen.⁷ If the product is exposed to freezing temperatures, defined as a temperature of less than or equal to 0°C or 32°F, it must be discarded. The manufacturer of Fluzone[®] does not have information on the extended stability of their product. The manufacturer recommends that when Fluzone[®] is drawn up into syringes, it is followed by immediate administration. Therefore, drawing vaccine into a syringe and storing it for future use is not recommended. Influenza vaccine that is drawn up in syringes the morning of influenza clinic to be administered the same morning at clinic is an acceptable practice. Of note, proper storage of the vaccine is still required (35°F-46°F or 2°C-8°C).

Influenza clinics will begin for CCHS employees on October 27, 2008, throughout the CCHS. Specifics regarding the scheduled influenza clinics throughout CCHS can be found on the Intranet at: <http://intranet.ccf.org/flu/info/>. Vaccine information statements should be distributed to all patients receiving the influenza vaccine. For a copy of the statement, refer to the following weblink: www.cdc.gov/vaccines/pubs/vis/downloads/vis-flu.pdf.

Conclusion: Influenza is a contagious disease that causes a considerable amount of morbidity and mortality. Vaccination against influenza is extremely important to protect against influenza. Annual influenza vaccination is recommended as vaccination during one influenza season does not provide protection from influenza in subsequent seasons. Influenza clinics are an opportunity for all health care providers and allied health personnel to get vaccinated against influenza in the interest of protecting themselves, their patients, and their families.

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Formulary Update

The Cleveland Clinic Pharmacy and Therapeutics Committee met in July 2008, and the following decision were made

Additions:

1) **Varenicline (Chantix®)**: It is FDA-approved for use as a treatment aid for smoking cessation. The initial adult dose is 0.5 mg once daily on days 1 through 3, and then, 0.5 mg twice daily on days 4 through 7. The maintenance dose (\geq Day 8) is 1 mg twice daily. In patients with $Cl_{cr} < 30$ mL/minute, the initial dose is 0.5 mg once daily with a maximum dose of 0.5 mg twice daily. **Note:** Start varenicline therapy 1 week before target quit date. **Varenicline use is restricted to Staff Physicians for initiation of therapy only (i.e., any prescriber may order varenicline for continuation of therapy).**

The rationale for the restriction is that the Staff Physician must weigh the risks versus benefits for the patient regarding the recent Food and Drug Administration (FDA) warning for initiation of therapy. The FDA has issued an update to the November, 2007 alert regarding postmarketing events reported with varenicline. After further review, the FDA feels that there is likely an association between varenicline and the neuropsychiatric events. The product labeling has been revised to include a warning concerning the neuropsychiatric symptoms, which usually occur during treatment, but have also occurred after varenicline treatment has been discontinued. Healthcare providers should monitor all patients taking varenicline for symptoms of serious neuropsychiatric events, including agitation, depression, suicidal behavior, and suicidal ideation.

2) **Imatinib (Gleevec®)**: It is FDA-approved for Gastrointestinal stromal tumors (GIST) kit-positive (CD117) unresectable and/or (metastatic) malignant; Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in chronic phase (newly-diagnosed); Ph+ CML in blast crisis, accelerated phase, or chronic phase after failure of interferon therapy; and Ph+ acute lymphoblastic leukemia (ALL; relapsed or refractory). The dose is dependent on the indication. Imatinib is available as 100- and 400-mg tablets. **Imatinib use is restricted to the Department of Hematology and Medical Oncology.**

3) **Bendamustine (Treanda®)**: It is FDA-approved for treatment of chronic lymphocytic leukemia (CLL). It is an injectable chemotherapy. **Bendamustine use is restricted to the Department of Hematology and Medical Oncology.**

4) **Methylnaltrexone (Relistor®)**: It is FDA-approved for treatment of opioid-induced constipation in patients with advanced illness receiving palliative care with inadequate response to conventional laxative regimens. Methylnaltrexone is a subcutaneous injection that is dosed according to body weight, and it is administered as one dose every other day as needed (maximum: 1 dose/24 hours). In patients with severe renal impairment ($Cl_{cr} < 30$ mL/minute), the dose is reduced by 50%. **Methylnaltrexone use is restricted to the Department of Hematology and Medical Oncology and Palliative Care Medicine.**

5) **Sevelamer carbonate (Renvela®)**: It is FDA-approved for the control of serum phosphorus in patients with chronic kidney disease who are on dialysis. This is the same FDA-approved indication as sevelamer hydrochloride (Renagel®). Renvela® is a new phosphorus binder developed to add a bicarbonate equivalent to the binder effect and decrease the GI symptoms that can limit binder use with kidney disease. In the near future, the manufacturer (Genzyme) intends to convert production of Renagel® to Renvela®. Therefore, Renvela® was added to the Formulary, and there will be a future implementation date for an automatic interchange from Renagel® to Renvela®.

6) **Histrelin (Supprelin LA®)**: It is FDA-approved for treatment of children with central precocious puberty (CPP). For children ≥ 2 years for CPP, a 50 mg implant is surgically inserted every 12 months, and therapy is discontinued at the appropriate time for the onset of puberty. **Histrelin use is restricted for pediatric patients that have a documented failure to Lupron®.**

7) **Clofarabine (Clolar®)**: It is FDA-approved for the treatment of pediatric patients 1 to 21 years of age with relapsed or refractory acute lymphoblastic leukemia (ALL) after failing at least two prior regimens. It is an injectable chemotherapy. **Clofarabine use is restricted to pediatric patients 1 to 21 years of age with relapsed or refractory acute lymphoblastic leukemia.**

Therapeutic Substitution:

There will be a therapeutic substitution for all extended-release nifedipine products (e.g., Procardia XL®, Adalat CC®, and generics). **All orders for an extended-release nifedipine product will be dispensed by the pharmacist as generic Adalat CC®.**

Restriction Changes:

- 1) **Cetuximab (Erbix®)**: Expanded restriction to include patients with non-small cell lung cancer.
- 2) **Rituximab (Rituxan®)**: There is an ABO Incompatible Kidney Transplantation Protocol that includes rituximab.
- 3) **Daclizumab (Zenapax®)**: There is an ABO Incompatible Kidney Transplantation Protocol that includes daclizumab.

Deletion:

1) **Chloral hydrate 500 mg suppositories**: Chloral hydrate 325 mg suppositories are discontinued by the manufacturer. The 500 mg suppositories present measurement challenges, and there are better alternatives available. If rectal chloral hydrate is needed, the liquid can be used rectally. This was a recommendation from The Children's Hospital P&T Committee.

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