

# Which Flu Shot is Better to Give: Intramuscular, Intranasal, or Intradermal?

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*There are no financial relationships that could be perceived as real or apparent conflicts of interest.*

**Universal Activity #:**

**2.0 Credit Hours (0.20 CEUs)**

**Objectives:**

- Recall major historical events that have led to the various formulations of influenza vaccine being available.
- Differentiate between antigenic drift and antigenic shift.
- Describe proper administration techniques of various formulations of influenza vaccine.
- Recognize key concepts to counsel different patient populations with regards to respective vaccine chosen.
- Compare and contrast key concepts associated with intramuscular, intranasal and intradermal influenza vaccines.

## Background

The influenza pandemic of 1918 is historically known as one of the most devastating battles man-kind has faced in its war with infectious disease<sup>1</sup>. Within one year, one-fifth of the world had been affected with the influenza virus<sup>1</sup>. There was more mortality with the influenza virus during this time (20 – 40 million deaths) than during the entire span of World War I<sup>1</sup>. Interestingly, the most common age of those who died of influenza during this time were 20 – 40 years of age<sup>1</sup>. Known commonly as the Spanish Flu, the virus was easily spread during this time due to the end of war, with armies of soldiers traveling the globe aboard ships and the celebration of Armistice Day that included large parties and parades<sup>1</sup>. The pandemic was so severe during this pre-vaccination period, that the life expectancy rate dropped by ten years<sup>1</sup>. Approximately 675,000 Americans died of influenza during this pandemic<sup>1</sup>. Finally, in 1945, the first influenza vaccine was developed and available to the public by 1946<sup>1</sup>.

Vaccines are made from harvesting the pathogen, in this case, the influenza virus, in a medium, such as chicken embryos<sup>2</sup>. Once the pathogen has reproduced in the medium, the antigens within the cell are then separated from the medium and isolated where it can be purified<sup>2</sup>. This process removes any parts of the medium that may still be present<sup>2</sup>. After purification, an adjuvant, commonly aluminum salt, is added in small amounts to the purified antigen to help increase the body's immune response<sup>2</sup>.

The influenza virus consists of two types of exterior proteins, neuraminidase and hemagglutinin<sup>3</sup>. Various strains of the virus are identified by these proteins<sup>3</sup>. Most commonly associated with flu outbreaks are three types of hemagglutinin (H1, H2, and H3) and two types of neuraminidase (N1 and N2)<sup>3</sup>. Strains within an antigenic subtype, such as H3N2, can vary annually<sup>3</sup>. There are two types of genetic alterations: antigenic drift and antigenic shift<sup>3</sup>. Once vaccination for various subtypes is initiated, their threat becomes limited; however, due to antigenic drift, various alterations and mutations of these surface proteins occur, causing the vaccine to have little to no effect on the newly created strain of the virus subtype as the human immune system no longer recognizes the surface proteins of the virus<sup>3</sup>. This can occur with both subtypes A and B<sup>4</sup>. Annual global observation helps identify new virulent strains and incorporates them into the following influenza vaccine<sup>4</sup>. This is why it is important to get vaccinated every year<sup>4</sup>. Antigenic shift consists of a newly created hemagglutinin and/or neuraminidase surface protein that occurs only in subtype A<sup>4</sup>. This shift occurs suddenly and is responsible for flu pandemics, such as the Spanish flu of 1918 and the swine flu of 2009.<sup>2-4</sup>

Infection of the influenza virus results in a contagious respiratory illness that can range from mild to severe<sup>5</sup>. During the pandemic of 1918, severe cases resulted in a rapid onset of an extremely viscous form of pneumonia that caused blocking of the airways<sup>1</sup>. Today, those who become infected with the flu will likely have a mild case, recovering on their own within two weeks<sup>5</sup>. Those considered high risk, however, could develop into a more serious case requiring medical attention. Young children, older adults, those with serious health conditions, and pregnant women are considered to be at high risk. Additionally, Alaskan Natives and American Indians tend to have an increased risk of developing complications from the flu.<sup>1,5</sup>

In the past, the annual influenza virus vaccines were administered either intramuscularly (inactivated virus) or intranasally (live attenuated)<sup>6</sup>. In May 2011, however, Sanofi Pasteur announced the FDA approval of Fluzone<sup>®</sup> Intradermal, which is administered within the dermal layer of the skin, the first of its kind in the US<sup>7</sup>. All types of influenza vaccines can be administered once the year's formulation is available, October through January<sup>5</sup>.

### ***Review of Intramuscular Administration***

#### **Introduction**

The earliest and most common method of administering the influenza virus vaccine is intramuscular (IM) administration. These formulations only contain the inactivated influenza virus (TIV) and thus development of the flu as result of the vaccine is not possible. There are several manufacturers that currently market an IM formulation. The table below shows a list of available formulations on the market and can vary based on the age of the patient. The use of the preservative, thimerosol, is used in multidose vials of Afluria<sup>®</sup>, Fluvirin<sup>®</sup>, and Fluzone<sup>®</sup> in reduced amounts<sup>8</sup>.

<b>Vaccine (IM only)</b>	<b>Indication (age)</b>	<b>Manufacturer</b>
<b>Agriflu<sup>®</sup></b>	18 and older	Novartis
<b>Fluzone<sup>®</sup></b>	6 months and older	Sanofi Pasteur
<b>Fluzone High Dose<sup>®</sup></b>	65 and older	Sanofi Pasteur
<b>Flulaval<sup>®</sup></b>	18 and older	ID Biomedical Corporation of Quebec
<b>Fluvirin<sup>®</sup></b>	4 and older	Novartis
<b>Fluarix<sup>®</sup></b>	3 and older	Glaxosmithkline
<b>Afluria<sup>®</sup></b>	6 months and older	CS Limited

The mechanism of action for intramuscular administration of the influenza vaccine is similar to the intradermal vaccine. Upon injection into the deltoid muscle, the influenza antigens are transported to the lymph nodes for antibody production<sup>3</sup>.

#### **Indication**

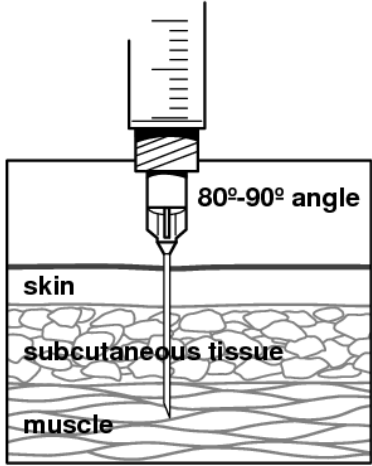
Patients who are six months to nine years of age should receive their vaccine in their physician's office as they require two doses of the age appropriate formulation, one month apart. Patients who are nine years of age or older need only one vaccination annually<sup>8</sup>.

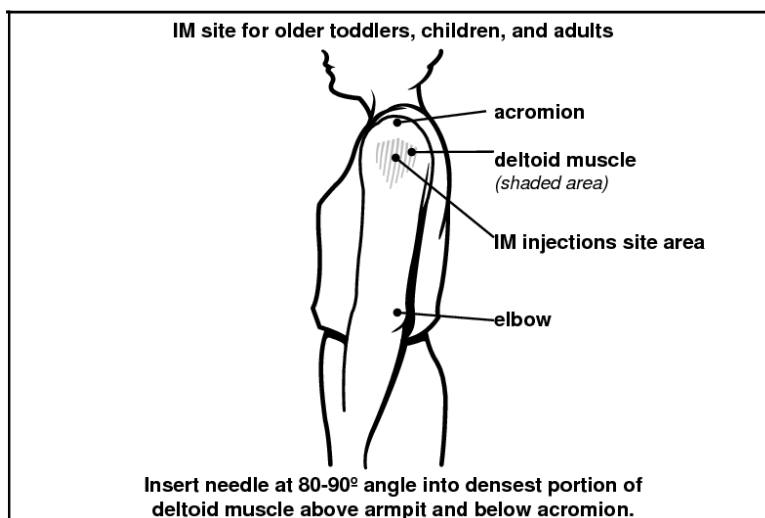
In 2010, Sanofi Pasteur developed a high dose formulation of their product, Fluzone<sup>®</sup>, to be used in patients who are 65 years or older. This formulation, which contains four times the amount of influenza antigens, was developed to induce a higher immune response in the elderly, who are at higher risk of complications from the

flu and commonly do not respond as well to regular formulations<sup>8</sup>. Studies have shown that a stronger immune response results from the higher dose, however, clinical trials are currently underway to determine whether the high dose formulation is effective in preventing illness<sup>5</sup>.

### Administration

To give the influenza vaccine intramuscularly, insert a 1-1.5 inch needle perpendicularly to the shoulder into the deltoid muscle of the arm<sup>9</sup>:

Needle insertion	
Use a needle long enough to reach deep into the muscle.	 A diagram showing a cross-section of the skin and underlying tissues. A syringe with a needle is shown inserted at an 80°-90° angle. The needle passes through the skin, subcutaneous tissue, and into the muscle. Labels include 'skin', 'subcutaneous tissue', and 'muscle'. The angle is labeled '80°-90° angle'.
Insert needle at an 80° to 90° angle to the skin with a quick thrust.	
Retain pressure on skin around injection site with thumb and index finger while needle is inserted.	
Aspiration before injection is not required.*(p.21)	
Multiple injections given in the same extremity should be separated as far as possible (preferably 1" to 1½" with minimum of 1" apart).	
*Red Book 2006, American Academy of Pediatrics	



### Adverse Reactions and Contraindications

Serious adverse reactions associated with the influenza vaccination are rare. More commonly, side effects associated with the vaccine include redness, pain and tenderness at the injection site<sup>10</sup>. Occasionally, systemic side effects may occur, which commonly consists of headache, malaise, and myalgia<sup>10</sup>. Those with a history of serious egg allergies should avoid this vaccine as eggs are used in development. One in a million patients vaccinated could result in the Guillain-Barre´ Syndrome<sup>10</sup>. Formulations should only be used in its approved age group<sup>10</sup>.

### Patient Counseling

Consult with the patient about the potential side effects, commonly redness, pain, and tenderness at the injection site<sup>10</sup>. Explain that the type of formulation used in intramuscular administration is inactivated and cannot cause

illness<sup>10</sup>. Be sure to ask the patient if they have an allergy to eggs, and if so, the symptoms associated with the allergic response<sup>10</sup>. Those who experience anaphylactic reactions should not receive the flu vaccine<sup>10</sup>. Advise the patient to consult their physician if they experience additional side effects, such as swelling or hives<sup>10</sup>.

## ***Review of Intranasal Administration***

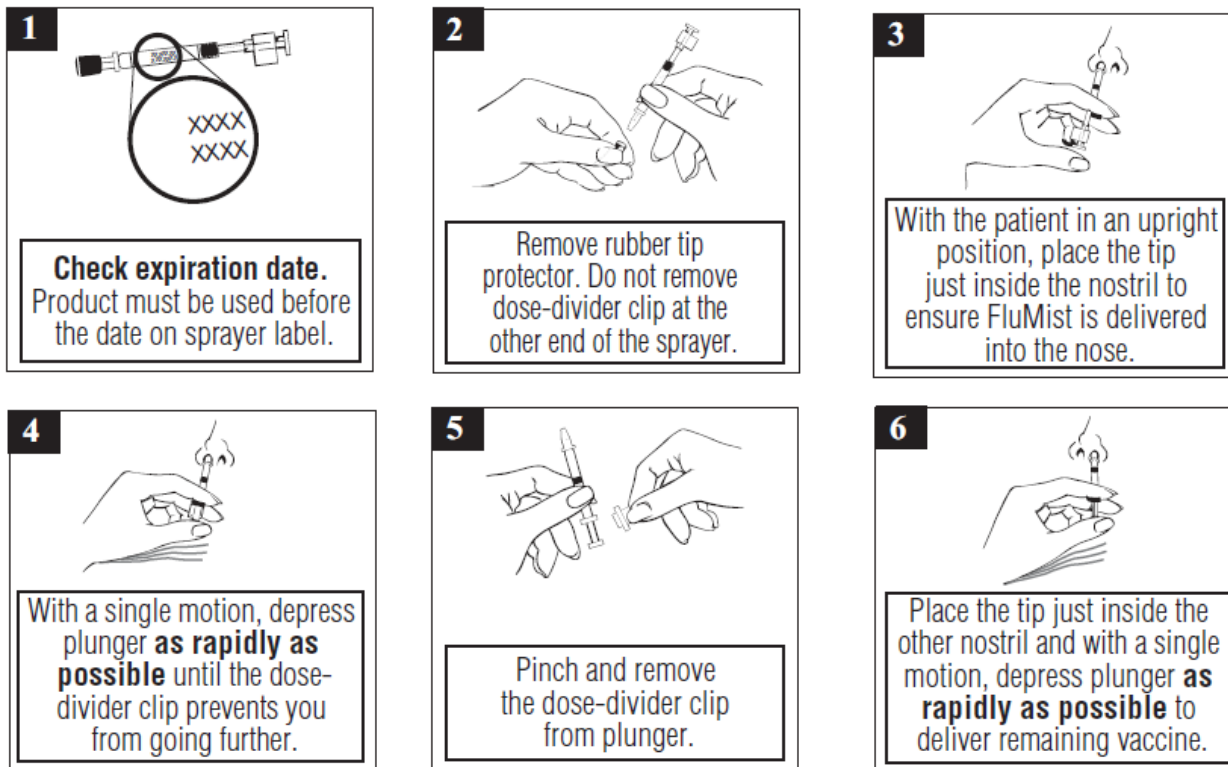
### **Introduction**

Currently, the only available intranasal influenza virus vaccine is Flumist<sup>®</sup>, manufactured by MedImmune Vaccines in 2003<sup>5</sup>. Unlike intramuscular formulations, intranasal formulations contain the first live influenza virus formulation approved for vaccination<sup>5</sup>. The live, attenuated virus (LAIV) is temperature sensitive, allowing it to replicate only within the nasal passages, not in the lungs<sup>5</sup>. It has been shown to be 86 percent effective in children and is advantageous to intramuscular administration as it is easier to administer and can potentially elicit a broader systemic and mucosal immune response compared to intramuscular formulations<sup>5</sup>. This formulation does not contain thimerosal<sup>5</sup>.

The mechanism of action for the influenza vaccine administered intranasally is similar to both intramuscular and intradermal administration, with a different site of action, by eliciting an immune response with the stimulation of antibodies<sup>6</sup>. Additionally, the mucosal antibody formation is also stimulated, potentially increasing cytotoxic T-cell formation<sup>6</sup>. Both intramuscular and intranasal vaccines are considered to be equally effective; however, no head-to-head clinical trials comparing the two exists<sup>8</sup>.

### **Administration**

The following diagram shows proper administration technique for administering the intranasal influenza vaccine and is taken from Flumist<sup>®</sup> Intranasal Spray prescribing information<sup>11</sup>:



### **Indication**

Flumist<sup>®</sup> is approved for the use in healthy patients aged two years through 49 years. It is administered with

one spray into each nostril to elicit an immune response and is to be given once annually. It is currently not approved for use in the elderly or in pregnant women<sup>11</sup>.

### Adverse Effects and Contraindications

In children, side effects include runny nose, wheezing, vomiting, headache and fever. For adults, runny nose, headache, sore throat and cough are commonly experienced<sup>1</sup>. Children who currently use aspirin or those under five years of age who have recurrent wheezing or asthma should not be given the intranasal formulation<sup>11</sup>. Currently, the intranasal formulation is not approved in pregnant women and patients 50 years of age and older<sup>5</sup>. Use should be avoided in those with a severe allergy to eggs. Those who have experienced Guillain-Barre´ Syndrome as a result of the influenza vaccine in the past should avoid vaccination.<sup>5</sup>

### Patient Counseling

Upon administration, that patient does not need to inhale (sniff)<sup>11</sup>. Consult with the patient about the potential side effects, commonly runny nose, sore throat, cough in adults; runny nose, wheezing, vomiting, headache or fever in children<sup>11</sup>. Explain that the type of formulation used in intranasal formulations is live, attenuated (weakened), meaning that the virus is live but is temperature sensitive and will not infect the lungs, causing illness. Aspirin should be avoided in children for at least four weeks following vaccination<sup>11</sup>. Be sure to ask the patient if they have an allergy to eggs, and if so, the symptoms associated with the allergic response<sup>11</sup>. Those who experience anaphylactic reactions should not receive any formulation of the flu vaccine<sup>11</sup>. Advise the patient to consult their physician if they experience additional side effects, such as swelling or hives<sup>11</sup>.

### *Intradermal Administration*

#### Introduction

Similar to other inactive influenza virus vaccines, Fluzone<sup>®</sup>Intradermal vaccine is trivalent, providing immunization against two A subtypes and one B subtype previously identified for 2011-2012 influenza vaccines<sup>7</sup>. Fluzone<sup>®</sup>Intradermal and all other vaccines manufactured for 2011-2012 season also include H1N1 strain, known to cause the swine flu<sup>7</sup>. This vaccine is packaged in a ready-to-use pre-filled microinjection system with an ultra-fine needle that is 90 percent smaller than needles used in intramuscular administration and contains less volume at 9mcg per 0.1ml dose, compared to the intramuscular dose of 15mcg per 0.5ml, while still providing effective immunogenicity<sup>7</sup>. In the past, intradermal vaccinations have shown to be effective in the tuberculin skin testing (Mantoux technique) and prevention of rabies. Intradermal vaccines are currently used globally including in Australia, Canada, and across Europe<sup>7</sup>.

Intradermal administration is thought to elicit a more effective immune response. The epidermis layer of the skin, primarily the stratum spinosum within the epidermis, contains vast amounts of dendritic cells<sup>12</sup>. Dendritic cells are a type of antigen-presenting cell (APC) that attach to protein antigens of microbes and carry them to surrounding lymph nodes<sup>3</sup>. The papillary layer of the dermis, located next to the stratum spinosum, contains both blood vessels and lymphatic vessels<sup>12</sup>. When the virus is injected into the dermal layer, the surrounding dendritic cells from the stratum spinosum transport the virus antigen through the lymphatic vessels in the papillary layer and present them to T lymphocytes, creating immunity<sup>3</sup>. According to a randomized, clinical trial published in the Journal of Infectious Diseases (2008), the intradermal route showed superiority in eliciting an immune response in the elderly compared to the commonly used intramuscular route<sup>13</sup>.

#### Indication

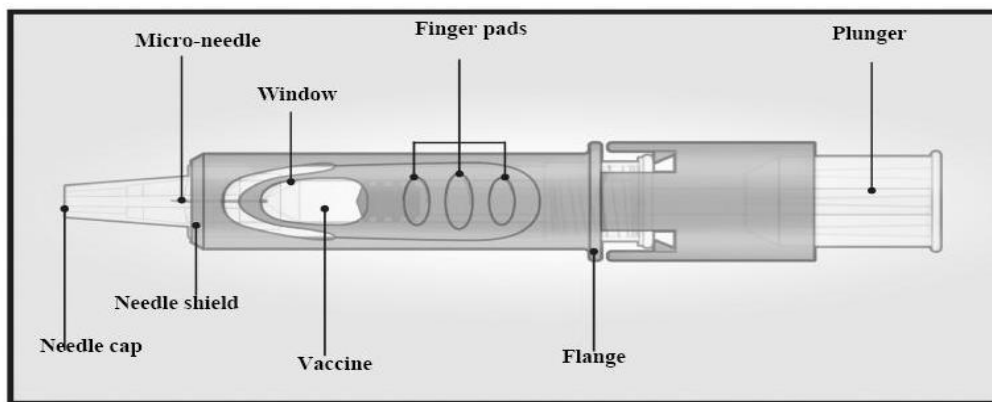
Fluzone<sup>®</sup> Intradermal is indicated in adults 18 – 64 years of age only<sup>10</sup>. It is pregnancy category B due to a

study performed in rabbits with a dose 20 times the normal human dose that resulted in no evidence of harm to fertility or fetus<sup>10</sup>. There are currently no human studies regarding the use of Fluzone<sup>®</sup> Intradermal in pregnant women<sup>10</sup>. There is a registry currently available for those who are pregnant and receive Fluzone<sup>®</sup> Intradermal<sup>10</sup>. Nursing mothers should proceed with caution as it is currently unknown if the vaccine is excreted in breast milk. Safety and efficacy has not been confirmed in those <18 years of age or those >64 years of age<sup>10</sup>. However, a randomized clinical trial published in 2008 showed efficacy in elderly adults, age 60 – 85 years, following intradermal influenza administration<sup>13</sup>.

### Administration

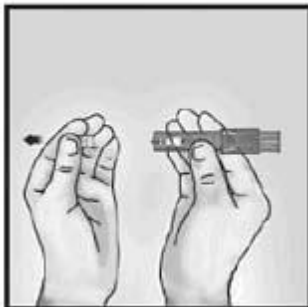
Only one dose of Fluzone<sup>®</sup> Intradermal (0.1ml) is required<sup>10</sup>. The Mantoux technique, a technique used in administering purified protein intradermally for tuberculin testing, is not required due to the pre-filled microinjection system. Directions for use are provided below, according to the Fluzone<sup>®</sup> Intradermal package insert<sup>10</sup>:

Gently shake the microinjection system before administering the vaccine.



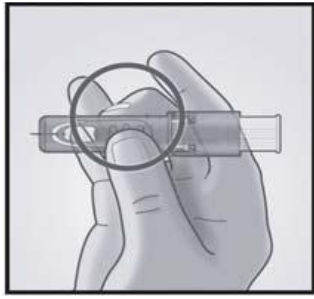
#### 1. Remove needle cap

Remove the needle cap from the microinjection system.



#### 2. Hold Microinjection System Between Thumb and Middle Finger

Hold the system by placing the thumb and middle finger only on the finger pads, the index finger remains free. Do not place fingers on the windows.



**3. Insert Needle Rapidly and Perpendicular to the Skin**

Insert the needle perpendicular to the skin, in the region of the deltoid, in a short, quick movement.



**4. Inject Using the Index Finger**

Once the needle has been inserted, maintain light pressure on the surface of the skin and inject using the index finger to push on the plunger. Do not aspirate.



**5. Remove Needle from Skin and Activate Needle Shield by Pushing Firmly on Plunger**

Remove the needle from the skin. Direct the needle away from you and others. With the same hand, push very firmly with the thumb on the plunger to activate the needle shield. You will hear a click when the shield extends to cover the needle.



### Adverse Effects and Contraindications

The most common adverse effects associated with Fluzone<sup>®</sup> Intradermal include erythema, induration (hardening of the skin), pain, swelling, and pruritis<sup>10</sup>. Other side effects reported in trials include malaise and ecchymosis (bruising) at the injection site<sup>13</sup>. The most common systemic effects include myalgia and headache.

In patients with a recent history of Guillain-Barre´ syndrome within the past six months, potential risks and benefits should be evaluated prior to administration<sup>10</sup>. Avoid use in those who have experienced a serious reaction to egg protein or any other influenza vaccine.

### Patient Counseling

It is important to remind the patient that Fluzone® Intradermal does not contain a live virus and cannot cause illness<sup>10</sup>. It is effective against the influenza virus only and does not prevent against other respiratory infections<sup>10</sup>. Be sure to ask the patient if they have ever had a serious allergic reaction to egg protein or other influenza vaccines<sup>10</sup>. The most common side effects are redness, swelling, hardening, pain, and itching at the injection site. Pregnant women should be informed of the registry available at Sanofi Pasteur, Inc<sup>10</sup>. All patients should report any side effects that they experience to their primary care physician or other health care provider<sup>10</sup>. Annual vaccination is recommended<sup>10</sup>.

### Summary

The development of the influenza vaccine made it possible to provide protection from infection. Annual mutations of the influenza virus occur, requiring seasonal vaccination for all patients. Three methods of administration are currently available and vary based on formulation and indication. It is important to understand the key differences in each formulation in order to provide effective patient care and be able to give an appropriate vaccine recommendation for each individual patient. The table below provides a summary of each method of administration previously discussed and their respective characteristics<sup>8,10,11</sup>:

Method of Administration	Brand Names	Site of Action	Contraindications / Exclusions	Common Side Effects	Patient Counseling Points
<b>Intramuscular (TIV-Trivalent Influenza Vaccine [inactive])<sup>1</sup></b>	Agriflu® Fluzone® Fluzone® (High Dose) Flulaval® Fluvirin® Fluarix® Afluria®	Deltoid Muscle	Egg allergy; Each formulation has its own approved age group, refer to each individual packaging for specific age indication.	Pain, tenderness, redness at injection site;	Pain and tenderness at injection site are common; Contact physician if serious signs of an allergic reaction occur.
<b>Intranasal (LAIV-Live - Attenuated Inactivated Virus)<sup>2</sup></b>	Flumist®	Nasal passages	Egg allergy; Children >5 yrs with asthma and history / recurrent wheezing; Avoid in patients >50 yrs and pregnant women.	Runny nose, headache, cough, sore throat (Children: Runny nose, wheezing, vomiting, headache, fever)	Avoid ASA use in children x 4 wks post-vaccination; Formulation cannot cause illness due to its temperature sensitive modification.
<b>Intradermal (TIV-Trivalent Influenza Vaccine [inactive])<sup>1</sup></b>	Fluzone® Intradermal	Dermis layer of the skin	Egg allergy; Avoid in children and elderly (over 65 yrs)	Redness, swelling, hardening, pain, itching	Inform pregnant women to online registry at Sanofi-Pasteur, Inc.

<sup>1</sup>Trivalent Influenza Vaccine (TIV): Inactivated virus used in vaccine formulation

<sup>2</sup>Live – Attenuated Inactivated Virus (LAIV): Modified to be temperature sensitive and is unable to replicate and grow in the lungs.

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# KENTUCKY IMMUNIZATION AUTHORITY FOR IMMUNIZATIONS

The following information is being provided for reference by pharmacists with respect to immunization authority under state law. For convenience, language related to immunizations has been underlined, and the change enacted by the Kentucky Legislature during 2011 is noted in bold text. A child is defined in other state statute as a person less than eighteen (18) years of age.

KRS 315. .010 (19) "Practice of pharmacy" means interpretation, evaluation, and implementation of medical orders and prescription drug orders; responsibility for dispensing prescription drug orders, including radioactive substances; participation in drug and drug-related device selection; administration of medications or biologics in the course of dispensing or maintaining a prescription drug order; the administration of adult immunizations pursuant to prescriber-approved protocols; the administration of influenza vaccines to individuals nine (9) to thirteen (13) years of age pursuant to prescriber-approved protocols with the consent of a parent or guardian; the administration of immunizations to individuals fourteen (14) to seventeen (17) years of age pursuant to prescriber-approved protocols with the consent of a parent or guardian; the administration of immunizations to a child as defined in KRS 214.032, pursuant to protocols as authorized by KRS 214.032, pursuant to protocols as authorized by KRS 315.500; drug evaluation, utilization, or regimen review; maintenance of patient pharmacy records; and provision of patient counseling and those professional acts, professional decisions, or professional services necessary to maintain and manage all areas of a patient's pharmacy-related care, including pharmacy-related primary care as defined in this section.