What’s New with the Flu in 2015-16?
Prevention, Diagnosis, and Treatment
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The influenza season is approaching in Colorado so it is important to vaccinate all children against influenza. New vaccines are available and new recommendations have been made for influenza vaccination. The composition of the new 2015-2016 seasonal influenza vaccine has changed, for both the trivalent and quadrivalent vaccines. Quadrivalent vaccines contain two influenza A strains and two B strains (Yamagata and Victoria lineage) whereas the trivalent products have only one influenza B strain. Quadrivalent formulations should provide better coverage when influenza B is prominent and both lineages circulate, although this is difficult to predict. Only LAIV is offered solely in quadrivalent form.

A reminder of the nomenclature follows:
- IIV=Inactivated Influenza Vaccine
- IIV₃=Inactivated Influenza Vaccine, Trivalent
- IIV₄=Inactivated Influenza Vaccine, Quadrivalent
- RIV=Recombinant Influenza Vaccine
- LAIV=Live-Attenuated Influenza Vaccine (FluMist ®)

For children aged 6 months to 18 years, the IIV and LAIV are the two types of vaccines available.

What are the recommendations for influenza vaccination?
Annual influenza vaccination is recommended for all persons 6 months of age and older. Ideally, vaccination should occur before the onset of influenza activity in the community. Based on data from 2013-2015, there is no longer a preference for LAIV over IIV for children aged 2 to 8 years. Influenza vaccination should not be delayed to acquire a specific vaccine preparation if another type is available.

Composition of vaccine
The composition of the seasonal 2015-16 influenza vaccine will be:

Trivalent Vaccines:
- A/California/7/2009 (H1N1) pdm09-like virus
- A/Switzerland/9715293/2013 (H3N2)virus
- B/Phuket/3073/2013-like virus (B/Yamagata lineage)

Quadrivalent vaccines:
- Will contain the above, plus a B/Brisbane/60/2008–like virus (Victoria lineage).

Influenza Vaccination Formulations for Children, 2015-16
There are many different vaccine formulations available. Some are licensed for specific age groups, or are more appropriate than others for persons with certain medical conditions. The influenza vaccines currently available are as follows:
Influenza Vaccination Formulations for Children, 2015-16

<table>
<thead>
<tr>
<th>Ages</th>
<th>Trade Name</th>
<th>Mfg</th>
<th>Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-35 mo</td>
<td>Fluzone® IIV3</td>
<td>sanofi pasteur</td>
<td>0.25mL single dose syringe</td>
</tr>
<tr>
<td></td>
<td>Fluzone® IIV4</td>
<td></td>
<td>5 mL multi-dose vial</td>
</tr>
<tr>
<td>2-49 yrs</td>
<td>FluMist® quadrivalent</td>
<td>MedImmune</td>
<td>0.2mL intranasal sprayer</td>
</tr>
<tr>
<td>≥3 yrs</td>
<td>Fluzone® IIV3</td>
<td>sanofi pasteur</td>
<td>5mL multi-dose vial</td>
</tr>
<tr>
<td></td>
<td>Fluzone® IIV4</td>
<td></td>
<td>0.5ml single-dose syringe</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5.0mL multidose vial</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.5mL single dose vial</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>syringe</td>
</tr>
<tr>
<td>≥3 yrs</td>
<td>Fluarix® IIV3 &amp; IIV4</td>
<td>GSK</td>
<td>0.5mL single dose syringe</td>
</tr>
<tr>
<td>≥4 yrs</td>
<td>Fluvarix® IIV3</td>
<td>Novartis</td>
<td>0.5mL single-dose syringe</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5.0 mL multidose vial</td>
</tr>
<tr>
<td>≥9 yrs*</td>
<td>Affuria® IIV3</td>
<td>CSL/ Merck</td>
<td>0.5mL single dose syringe</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5.0mL multidose vial</td>
</tr>
<tr>
<td>≥3 yrs</td>
<td>FluLaval IIV3 &amp; IIV4</td>
<td>GSK</td>
<td>0.5mL single-dose syringe</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5.0mL multidose vial</td>
</tr>
</tbody>
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*Licensed for 5 years and older, ACIP recommends 9 and older.

Vaccine Formulations for Adults, 2015-16

<table>
<thead>
<tr>
<th>Ages</th>
<th>Trade Name</th>
<th>Mfg</th>
<th>Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥18 yrs</td>
<td>Flucelvax® IIV3</td>
<td>Novartis</td>
<td>0.5mL single-dose syringe</td>
</tr>
<tr>
<td>≥18-64 yrs</td>
<td>FluBlock® Recombinant IIV3</td>
<td>Protein sciences</td>
<td>0.5mL single-dose syringe</td>
</tr>
<tr>
<td>18-64 yrs</td>
<td>Fluzone® Intradermal IIV3</td>
<td>sanofi pasteur</td>
<td>0.1mL microinjection system</td>
</tr>
<tr>
<td>≥65 yrs</td>
<td>Fluzone® High Dose IIV3</td>
<td>sanofi pasteur</td>
<td>0.5mL single-dose syringe</td>
</tr>
</tbody>
</table>

Frequently Asked Questions

**Which pediatric patients will need two doses of influenza vaccine for the 2015-16 influenza season?**

Children aged 6 months through 8 years will need 2 doses of vaccine administered at least 4 weeks apart during their first season of vaccination. Due to the change in the vaccine composition for 2015-2016, there has been a change in recommendations for children in this age group who have received prior vaccination. Children aged 6 months through 8 years who have received at least 2 doses of influenza vaccine previously only require 1 dose for the 2015-2016 season. (figure). The two previous doses do not need to have been given during the same season or consecutive seasons.

http://www.cdc.gov/flu/professionals/acip/app/figure1.htm
What does the CDC recommend for patients with egg allergies?

1. Individuals with a history of egg allergy who have experienced only hives after exposure to egg can receive influenza vaccine. Because relatively little data are available for use of LAIV in this setting, IIV or RIV should be used. RIV is egg-free and may be used for persons aged 18-49 years who have no other contraindications. However, IIV (egg- or cell-culture based) may also be used, with the following additional safety measures:
   - Vaccine should be administered by a healthcare provider who is familiar with the potential manifestations of egg allergy; and
   - Vaccine recipients should be observed for at least 30 minutes for signs of a reaction after administration of each vaccine dose (1).

2. Persons who report having had reactions to egg involving such symptoms as angioedema, respiratory distress, lightheadedness, or recurrent emesis; or who required epinephrine or another emergency medical intervention may receive RIV3, if aged 18 through 49 years and there are no other contraindications. If RIV3 is not available or the recipient is not within the indicated age range, IIV should be administered by a medical provider with experience in the management of severe allergic conditions.

3. All vaccines should be administered in settings in which personnel and equipment for rapid recognition and treatment of anaphylaxis are available.

4. Some persons who report allergy to egg might not be egg-allergic. Those who are able to eat lightly cooked egg (e.g., scrambled egg) without reaction are unlikely to be allergic. Egg-allergic persons might tolerate egg in baked products (e.g., bread or cake). Tolerance to egg-containing foods does not exclude the possibility of egg allergy (2). Egg allergy can be confirmed by a consistent medical history of adverse reactions to eggs and egg-containing foods, plus skin and/or blood testing for immunoglobulin E antibodies to egg proteins.

5. For individuals who have no known history of exposure to egg, but who are suspected of being egg-allergic on the basis of previously performed allergy testing, consultation with a physician with expertise in the management of allergic conditions should be obtained prior to vaccination. Alternatively, RIV3 may be administered if the recipient is aged 18 through 49 years.

A previous severe allergic reaction to influenza vaccine, regardless of the component suspected to be responsible for the reaction, is a contraindication to future receipt of the vaccine.

Flu vaccine FAQs for Children’s Hospital Colorado

Which influenza vaccines are available at Children’s? Vaccines are ordered every spring from our distributor to ensure an adequate supply for patients, families and staff. We have individual syringes of Fluzone® and Fluarix® quadrivalent injectable vaccine for patients 6 months-35 months and > 3 years of age. All LAIV4 (FluMist®) for eligible patients aged 2 to 49 years is quadrivalent.

A grant from the Association of Volunteers and a generous foundation donation has enabled us to vaccinate family members against influenza without cost. Our family influenza vaccine vials are quadrivalent influenza vaccine made by sanofi pasteur. We do not have LAIV4 (FluMist®) available for family vaccine.

Who can receive LAIV4 (Flumist®) vaccination? Healthy individuals aged between 2 and 49 years of age can receive LAIV4. It is contraindicated in people with a history of severe allergic reaction to any vaccine component, or after a previous dose of any influenza vaccine, or for those with anaphylaxis to eggs. The effectiveness or safety have not been established in children and adults who have chronic pulmonary, cardiovascular (except isolated hypertension), renal, hepatic, neurologic/neuromuscular, hematologic, or metabolic disorders, and those who have immunosuppression. The AAP recommends not using LAIV in children with asthma, or children aged 2-4 years old with a history of recurrent wheezing or a wheezing episode in the previous 12 months; close contacts/ caregivers of severely immunosuppressed persons who require a protected environment; and pregnant women. The vaccine may not be as effective in children with nasal congestion (as it may impede vaccine delivery), those who have received live virus vaccines within the past 4 weeks, and those on an influenza antiviral medication at the time of vaccination.
If quadrivalent vaccine includes one additional strain, why isn’t it preferred for use over trivalent vaccine?

Even though both influenza B viruses are likely to cause disease during an influenza season, traditionally experts needed to choose between the two very different B viruses to include with the two A viruses based on what B virus is expected to predominate. This can be difficult to predict. The quadrivalent vaccine that will be available for the 2015-16 season includes both B viruses. Currently, the ACIP does not express a preference for quadrivalent over trivalent for persons for whom more than one type of vaccine is indicated and available. Vaccination should not be delayed in order to obtain a specific product.

Does LAIV protect against H1N1?

Vaccine effectiveness data from the 2013-2014 season showed that LAIV was not as good for H1N1 as the IIV. Since the same vaccine is being used for this year, this may be the case for this season. The reasons behind the LAIV’s lack of effectiveness against H1N1 infections during the 2013-2014 season are not fully understood, and the CDC is continuing to monitor surveillance data closely. Early data for the 2015-2016 season show that there is a good match between the vaccine strains and circulating strains.

Influenza Testing and Treatment

This section focuses on how to diagnose and treat influenza. It is abstracted from, and is in agreement with current CDC guidelines and AAP recommendations.1,2

1. How do I test for influenza?

   This winter, Children’s Hospital Colorado will again have two laboratory tests for influenza virus, the influenza-only polymerase chain reaction (PCR) and a comprehensive Respiratory Pathogen PCR. PCRs are significantly more sensitive than rapid influenza antigen detection tests (>95% vs. 10-70%, respectively).

   ▶ Influenza PCR detects influenza A and influenza B and provides the influenza A 2009 H1N1 subtype. It is run 24/7 during flu season, with most results available in 3 hours on average once specimens arrive at the Anschutz Campus. Only nasopharyngeal (NP) aspirates or NP flocked swabs can be tested.

   ▶ The comprehensive Respiratory Pathogen PCR (RVP) detects influenza A and its two subtypes (H3N2 or 2009 H1N1) and influenza B, as well as other respiratory viruses and bacteria. It is now performed only by FilmArray®, which provides results in about 3 hours once specimens arrive at the Anschutz Campus. Many respiratory specimen types can be tested, including NP flocked swabs, NP aspirates, tracheal aspirates, bronchoalveolar lavage, and lung tissue.

2. Who should I test for influenza?

   In general, influenza tests should be ordered only if positive or negative results will influence clinical management or influence the clinical practice for other patients. PCRs are very expensive, with the charge for Respiratory Pathogen PCR about four times higher than for influenza only-PCR, despite no significant difference in detection of influenza viruses between the two tests. Therefore, who to test and test choice depends on the clinical situation, as well what viruses are circulating in the community. It is important to recognize that numerous viruses can present similar to influenza and that an influenza test is more likely to be positive during the peak of influenza season (increased pretest probability).

   Have a higher consideration for influenza on your differential if:

   • Patient presents with classic flu symptoms (usually older patients): high fever, chills, sweats, myalgia, photophobia, headache, dry cough
   • Exposure to someone with proven influenza or with classic flu symptoms
   • Patient with high fever without focus and symptoms not typical of other viral illnesses circulating at the time (e.g. bronchiolitis, URI, viral pneumonia)
   • Patient/family not vaccinated
   • Patient not already on oseltamivir

   Our current recommendations for test ordering are depicted on the following chart:
3. **Who should be treated for presumed or proven influenza?**
   
a. Clinical trials and observational data show that early antiviral treatment can shorten the duration of fever and illness symptoms, and may reduce the risk of complications from influenza (e.g., otitis media in young children, pneumonia, respiratory failure) and death, and shorten the duration of hospitalization. Clinical benefit is greatest when antiviral treatment is administered early, especially within 48 hours of influenza illness onset.

b. Treatment should not wait for laboratory confirmation of influenza but, when clinically indicated, should be started as soon as possible.

c. Antiviral treatment is recommended as early as possible for any patient with confirmed or suspected influenza who:
   1) is hospitalized;
   2) has severe, complicated, or progressive illness; or
   3) is an outpatient who is at higher risk for influenza complications (see box) on the basis of their age or underlying medical conditions. Clinical judgment, based on the patient’s disease severity and progression, age, underlying medical conditions, likelihood of influenza, and time since onset of symptoms, is important when making antiviral treatment decisions for high-risk outpatients.

d. Antiviral treatment should be considered for any outpatient with confirmed or suspected influenza who is otherwise healthy for whom a decrease in duration of clinical symptoms is felt to be warranted by his or her treating provider, if treatment can be initiated within 48 hours of illness onset.
4. When is it too late to treat someone for influenza?
CDC guidelines state that when indicated, antiviral treatment should be started as soon as possible after illness onset, ideally within 48 hours of symptom onset. However, observational studies suggest that antiviral treatment might still be beneficial in patients with severe, complicated or progressive illness and in hospitalized patients when even if started 48 hours after illness onset. The Children’s Hospital Colorado ID group recommends that you strongly consider antiviral treatment for anyone with severe influenza disease regardless of the day of illness.

5. How do I treat influenza?
Neuraminidase Inhibitors Oseltamivir (Tamiflu®) and zanamivir (Relenza®) are the antiviral medications still recommended for treatment and chemoprophylaxis of influenza A and influenza B virus infections, as virtually all US influenza viruses characterized from last winter were susceptible in vitro to them. They are classified as neuraminidase inhibitors (NAIs) because they inhibit the viral neuraminidase enzyme that helps progeny escape from infected cells. NAIs may also have efficacy against the novel influenza viruses.

<table>
<thead>
<tr>
<th>AGE</th>
<th>TREATMENT DOSE</th>
<th>PROPHYLAXIS DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 weeks - 3 months&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3 mg/kg/dose &lt;b&gt;twice&lt;/b&gt; a day</td>
<td>Not recommended unless situation judged critical</td>
</tr>
<tr>
<td>Children 3-11 months&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3 mg/kg/dose &lt;b&gt;twice&lt;/b&gt; a day</td>
<td>3 mg/kg/dose once daily</td>
</tr>
<tr>
<td>Children 1-12 years old and weighing:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 15 kg</td>
<td>30 mg/dose &lt;b&gt;twice&lt;/b&gt; a day</td>
<td>30 mg once daily</td>
</tr>
<tr>
<td>&gt; 15-23 kg</td>
<td>45 mg/dose &lt;b&gt;twice&lt;/b&gt; a day</td>
<td>45 mg once daily</td>
</tr>
<tr>
<td>&gt;23-40 kg</td>
<td>60 mg/dose &lt;b&gt;twice&lt;/b&gt; a day</td>
<td>60 mg once daily</td>
</tr>
<tr>
<td>&gt;40 kg</td>
<td>75 mg/dose &lt;b&gt;twice&lt;/b&gt; a day</td>
<td>75 mg once daily</td>
</tr>
<tr>
<td>Children &gt; 13 years of age and adults</td>
<td>75 mg/dose &lt;b&gt;twice&lt;/b&gt; a day</td>
<td>75 mg once daily</td>
</tr>
</tbody>
</table>

*Although not part of the FDA-approved indications, use of oral oseltamivir for treatment of influenza in infants less than 14 days old, and for chemoprophylaxis in infants 3 months to 1 year of age, is recommended by the CDC and the American Academy of Pediatrics.

The American Academy of Pediatrics has recommended an oseltamivir treatment dose of 3.5 mg/kg orally twice daily for infants aged 9-11 months for the 2013-14 season, on the basis of data which indicated that a higher dose of 3.5 mg/kg was needed to achieve the protocol-defined targeted exposure for this cohort as defined in the CASG 114 study (Kimberlin, 2013). It is unknown whether this higher dose will improve efficacy or prevent the development of antiviral resistance. However, there is no evidence that the 3.5 mg/kg dose is harmful or causes more adverse events to infants in this age group.

*Although all children aged younger than 5 years are considered at higher risk for complications from influenza, the highest risk is for those aged younger than 2 years, with the highest hospitalization and death rates among infants aged younger than 6 months.
Oseltamivir (Tamiflu®) is given orally for 5 days with dose adjustments required for renal impairment and weight. Longer treatment courses (i.e., 10-14 days) can be considered for patients who remain severely ill after 5 days of treatment. The commercially manufactured liquid formulation of oseltamivir has a concentration of 6 mg/mL. The most common side effects of oseltamivir are nausea or vomiting. Transient neuropsychiatric events (self-injury or delirium) have been reported, mainly among Japanese adolescents and adults. Recommended dosing for treatment or prophylaxis for children by age and weight is summarized below:

Zanamivir (Relenza®) is a dry powder administered via oral inhalation. It is not FDA-cleared for treatment in children under 7 years of age. The dose is two breath-activated inhalations twice daily for 5 days. The prophylaxis dose is 2 inhalations once daily for 5 yrs of age and older. It is not recommended for patients with underlying airway disease including asthma or COPD because of a lack of safety and efficacy data in these individuals. Serious adverse events including bronchospasm and decline in lung function have been reported with zanamivir use, most commonly in patients with underlying airway disease. (If zanamivir is used in patients with underlying airway disease, they should be instructed to have a fast-acting bronchodilator available). Allergic reactions including rashes and oropharyngeal or facial edema are reported. Side effects can be diarrhea, nausea, sinusitis, runny or stuffy nose, bronchitis, cough, headache, dizziness, and ear, nose and throat complaints.

Amantadine/Rimantadine: These are not currently recommended for antiviral treatment of chemoprophylaxis, since most circulating influenza A strains have developed resistance to these drugs.

Peramavir (Rapivab®) is the third neuraminidase inhibitor approved to treat influenza infection but is the only agent in its class available in IV form. It has been approved by the FDA for use in individuals 18 years of age and older.

Investigational drugs: Parenterally-administered zanamivir (another neuraminidase inhibitor) was used with variable success for treatment of severely-ill patients during the pH1N1 pandemic. These medications remain in clinical trials, and are limited outcomes data available at this time.

Bacterial co-infections: Patients with influenza are at high risk for secondary bacterial complications like bacterial pneumonia. Antibacterial therapy plus antiviral treatment are recommended for patients with community-acquired pneumonia when influenza also is suspected. Antibiotic treatment should be directed at likely bacterial pathogens most often associated with influenza such as S. pneumoniae, S. pyogenes, and S. aureus, including methicillin-resistant (MRSA), especially for hospitalized patients.

Chemoprophylaxis: Neuraminidase inhibitors are 70-90% effective in preventing influenza. Yet the CDC does not recommend widespread or routine use of chemoprophylaxis due to the possibility that resistant viruses could emerge, thus limiting the usefulness of these medications for high-risk or severely ill persons. Annual vaccination is a better way to prevent influenza because vaccines can be given well before exposures occur and can provide safe and effective immunity throughout the influenza season if the vaccine and circulating strains are well-matched.

Chemoprophylaxis is not usually recommended if more than 48 hours have elapsed since the last exposure to an infected person. Persons receiving chemoprophylaxis should be encouraged to seek medical attention as soon as they develop a febrile respiratory illness that might indicate influenza. For effective prophylaxis, an antiviral medication must be taken each day for the duration of potential exposure to a person with influenza, and continued for 7 days after the last known exposure. Post exposure prophylaxis should be considered for family members and close contacts of infected patients if they are at high risk of complications from influenza (see risk table above).

Recommendations for the care of ED patients suspected of having influenza can be found on the department of epidemiology intranet site.

References:
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