Update—Influenza Vaccination and Antiviral Recommendations

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IHS Call
23 September 2015
Overview

- Update on 2015-16 ACIP influenza vaccination recommendations

- Very brief overview of indications for antiviral treatment for influenza
2015-16 ACIP Influenza Vaccination Statement


- Annual influenza vaccination is recommended for all persons aged 6 months and older

- Topics discussed:
  - Influenza vaccine virus composition for 2015-16
  - New FDA-approvals since the 2014-15 statement
  - Update in dosing algorithm for children aged 6 mos. through 8 yrs.
  - Updated recommendations regarding use of LAIV and IIV for healthy 2 through 8 year olds, including removal of LAIV preference

- For topics not addressed, refer to 2013-14 statement
Vaccine Composition for 2015-16

Two strain changes compared with the 2014-15:

- For trivalent vaccines,
  - an A/California/7/2009 (H1N1)pdm09-like virus (same as 2014-15);
  - An A/Switzerland/9715293/2013 (H3N2)-like virus (replaces A/Texas/50/2012 (H3N2)-like)
  - A B/Phuket/3073/2013-like virus (Yamagata lineage; replaces previous B/Massachusetts/2/2012-like Yamagata lineage virus)

- For quadrivalent vaccines,
  - The above three viruses and a B/Brisbane/60/2008-like virus (Victoria lineage; same as 2014-15)
<table>
<thead>
<tr>
<th>Trade name</th>
<th>Manufacturer</th>
<th>Presentation</th>
<th>Mercury (from thimerosal) μg/0.5 mL</th>
<th>Ovalbumin μg/0.5 mL</th>
<th>Age Indications</th>
<th>Latex</th>
<th>Route</th>
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<tbody>
<tr>
<td>Inactivated influenza vaccine, quadrivalent (IV4), standard dose</td>
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<tr>
<td>Contaminations*: Severe allergic reaction to any vaccine component, including egg protein, or after previous dose of any influenza vaccine. Precautions**: Moderate to severe acute illness with or without fever; history of Guillain-Barré syndrome within 6 weeks of receipt of influenza vaccine.</td>
<td>Fluarix Quadrivalent</td>
<td>GlaxoSmithKline</td>
<td>0.5 mL single-dose prefilled syringe</td>
<td>—</td>
<td>≤0.05</td>
<td>≥3 yrs</td>
<td>No IM†</td>
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<tr>
<td>FluLaval Quadrivalent</td>
<td>ID Biomedical Corp. of Quebec (distributed by GlaxoSmithKline)</td>
<td>5.0 mL multi-dose vial</td>
<td>&lt;25</td>
<td>≤0.3</td>
<td>3 yrs</td>
<td>No IM†</td>
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<tr>
<td>Fluzone Quadrivalent</td>
<td>Sanofi Pasteur</td>
<td>0.25 mL single-dose prefilled syringe</td>
<td>—</td>
<td>$</td>
<td>6 through 35 mos</td>
<td>No IM†</td>
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<tr>
<td>Fluzone Intradermal Quadrivalent</td>
<td>Sanofi Pasteur</td>
<td>microinjection system</td>
<td>0.1 mL single-dose prefilled syringe</td>
<td>—</td>
<td>$</td>
<td>6 through 64 yrs</td>
<td>No IM†</td>
</tr>
<tr>
<td>Inactivated influenza vaccine, trivalent (IV3), standard dose</td>
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<tr>
<td>Contaminations*: Severe allergic reaction to any vaccine component, including egg protein, or after previous dose of any influenza vaccine. Precautions**: Moderate to severe acute illness with or without fever; history of Guillain-Barré syndrome within 6 weeks of receipt of influenza vaccine.</td>
<td>Afluria</td>
<td>bioCSL</td>
<td>0.5 mL single-dose prefilled syringe</td>
<td>—</td>
<td>≤1</td>
<td>≥9 yrs†</td>
<td>No IM†</td>
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<td></td>
<td></td>
<td></td>
<td>5.0 mL multi-dose vial</td>
<td>24.5</td>
<td>≤1</td>
<td>≥9 yrs† via needle; 18 through 64 yrs via jet injector</td>
<td>No IM†</td>
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<td></td>
<td>Fluvin</td>
<td>Novartis Vaccines and Diagnostics</td>
<td>0.5 mL single-dose prefilled syringe</td>
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<td></td>
<td></td>
<td></td>
<td>5.0 mL multi-dose vial</td>
<td>25</td>
<td>≤1</td>
<td>≥4 yrs</td>
<td>No IM†</td>
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<td>Fluzone</td>
<td>Sanofi Pasteur</td>
<td>0.25 mL single-dose prefilled syringe</td>
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<td></td>
<td>5.0 mL multi-dose vial</td>
<td>25</td>
<td>$</td>
<td>≥6 mos</td>
<td>No IM†</td>
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<tr>
<td>Inactivated influenza vaccine, cell-culture-based (cIV3), standard dose</td>
<td></td>
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<td>Contaminations*: Severe allergic reaction to any vaccine component, including egg protein, or after previous dose of any influenza vaccine. Precautions**: Moderate to severe acute illness with or without fever; history of Guillain-Barré syndrome within 6 weeks of receipt of influenza vaccine.</td>
<td>Fluclervax</td>
<td>Novartis Vaccines and Diagnostics</td>
<td>0.5 mL single-dose prefilled syringe</td>
<td>—</td>
<td>≥18 yrs</td>
<td>Yes** IM†</td>
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<td>Inactivated influenza vaccine, trivalent (IV3), high dose</td>
<td></td>
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<tr>
<td>Contaminations*: Severe allergic reaction to any vaccine component, including egg protein, or after previous dose of any influenza vaccine. Precautions**: Moderate to severe acute illness with or without fever; history of Guillain-Barré syndrome within 6 weeks of receipt of influenza vaccine.</td>
<td>Fluzone High-Dose***</td>
<td>Sanofi Pasteur</td>
<td>0.5 mL single-dose prefilled syringe</td>
<td>—</td>
<td>≥65 yrs</td>
<td>No IM†</td>
<td></td>
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<td>Recombinant influenza vaccine, trivalent (RIV3), standard dose</td>
<td></td>
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<tr>
<td>Contaminations*: Severe allergic reaction to any vaccine component. Precautions**: Moderate to severe acute illness with or without fever; history of Guillain-Barré syndrome within 6 weeks of receipt of influenza vaccine.</td>
<td>FluBlok</td>
<td>Protein Sciences</td>
<td>0.5 mL single-dose vial</td>
<td>0</td>
<td>≥18 yrs</td>
<td>No IM†</td>
<td></td>
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<td>Live attenuated influenza vaccine, quadrivalent (LAIV4)</td>
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<tr>
<td>Contaminations*: Severe allergic reaction to any vaccine component, including egg protein, or after previous dose of any influenza vaccine. Concomitant use of aspirin or aspirin-containing medications in children and adolescents. In addition, ACP recommends LAIV4 not be used for pregnant women, immunosuppressed persons, persons with egg allergy, and children aged 2 through 4 years who have asthma or who have had a wheezing episode noted in the medical record within the past 12 months, or for whom parents report that a health care provider stated that they had wheezing or asthma within the last 12 months. LAIV4 should not be administered to persons who have taken influenza antiviral medications within the previous 48 hours. Persons who care for severely immunosuppressed persons who require a protective environment should not receive LAIV4, or should avoid contact with such persons for 7 days after receipt. Precautions**: Moderate to severe acute illness with or without fever; history of Guillain-Barré syndrome within 6 weeks of receipt of influenza vaccine; asthma in persons aged 5 years and older; medical conditions which might predispose to higher risk for complications attributable to influenza.</td>
<td>FluMist Quadrivalent†††</td>
<td>MedImmune</td>
<td>0.2 mL single-dose prefilled intranasal sprayer</td>
<td>—</td>
<td>&lt;0.24 (per 0.2 mL)</td>
<td>2 through 49 yrs</td>
<td>No IN</td>
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</table>

See table footnotes on page next page.
Influenza Vaccine Product Updates for 2015-16

New licensures, labeling information, and other changes:

- **Fluzone® Intradermal Quadrivalent IIV**
  - Replaces previous trivalent formulation of Fluzone Intradermal
  - Non-inferior immunogenicity, similar adverse event profile to trivalent

- **Expanded age indication for Flublok® (now 18 and older)**
  - Previously licensed for 18 through 49 years
  - Similar immunogenicity and safety among persons 50 years and over

- **Approval of administration of Afluria® by Stratis® jet injector for persons 18 through 64 years of age**
  - Ages 9 through 17 years, 65 years and over—needle/syringe only
  - ACIP does not recommend Afluria under 9 years
  - No other influenza vaccines currently licensed for use with a jet injector

- **Some presentation changes**
  - Flulaval and Fluarix trivalents no longer available (quadrivalents only)
  - Fluzone standard dose trivalent still available, but only multidose vial (quadrivalent available in all four presentations)

*MMWR (2015) 64;30: 618-625*
Available Influenza Vaccine Products, 2015-16
General Characteristics

- Live virus vs. not
- Trivalent vs. quadrivalent
- Standard-dose vs. high-dose
- Egg-based vs. non-egg based
- Intramuscular vs. intradermal vs. intranasal
Currently Available Influenza Vaccines (N=11)
Common Features

- Contain hemagglutinin (HA) derived from
  - an Influenza A(H1N1) virus,
  - an Influenza A(H3N2) virus, and
  - One (if trivalent) or two (if quadrivalent) Influenza B viruses
Available Influenza Vaccine Products, 2015-16
(11 Branded Products)

- **9 inactivated vaccine products (IIVs)**
  - 4 quadrivalent
    - All standard dose, all egg-based
    - 3 intramuscular, 1 intradermal
  - 3 trivalent, standard dose, egg-based (IIV3)—intramuscular
  - 1 trivalent, standard dose, cell culture-based (ccIIV3)—intramuscular
  - 1 trivalent, high dose, egg based (high dose IIV3)—intramuscular

- **1 live attenuated vaccine product (LAIV)**
  - Quadrivalent only (LAIV4)—intranasal

- **1 recombinant vaccine product (RIV)**
  - Trivalent only (RIV3)—intramuscular
Trivalent Inactivated Influenza Vaccines (IIV3s)

- Have different age indications; need to check package insert
  - An age-appropriate product should be used
  - Products available for persons as young as 6 months
- All are egg-based EXCEPT Flucelvax® (Novartis)—MDCK cells
- All contain 15µg of HA per virus EXCEPT Fluzone® High-Dose
  - Contains 60µg HA per virus
  - Approved for persons aged 65 years and older
  - 24.2% more effective than standard dose IIV3 in preventing lab confirmed influenza among persons 65 and older in one RCT
- All are administered intramuscularly (needle/syringe)
- One (Afluria®, bioCSL) approved for administration via jet injector
  - May be administered by sterile needle and syringe (ages 9 and older),
  - OR by Stratis® (PharmaJet) jet injector (ages 18 through 64 years ONLY)
Quadrivalent Inactivated Influenza Vaccines (IIV4s)

- Provide broader protection against Influenza B viruses
  - There are two Influenza B lineages: Victoria and Yamagata
  - Immunization against virus from one lineage provides only limited cross-protection against viruses in the other
  - Predominant lineage difficult to predict ahead of each season
  - *Trivalent vaccines contain only one B vaccine virus*
  - *Quadrivalents contain two B viruses (one from each lineage)*

- All contain 15µg of HA per virus EXCEPT Fluzone® Intradermal Quadrivalent

- All are administered intramuscularly EXCEPT Fluzone Intradermal Quadrivalent (intradermal)
  - *Administered with device included in packaging*
  - 9 mcg per HA virus

- Three different products; one approved for as young as 6 mos
Vaccines Produced via Non-Egg-Based Technologies

- May permit more rapid scale up of vaccine production (e.g., as might be needed during a pandemic)

- Two vaccines this season, both only trivalents currently:
  - Cell culture-based
  - Recombinant HA
Cell Culture-Based Inactivated Influenza Vaccine (ccIIV3)

- **Flucelvax® (Novartis)**
- Approved for persons aged 18 and older
- Licensed in the U.S. in 2012; in the EU since 2007
- Currently available only in a trivalent formulation
- Vaccine viruses propagated in Madin-Darby Canine Kidney cells rather than in eggs
- However, initial reference strains are passaged in eggs
  - Cannot be considered egg-free in the U.S.
  - Per mfr, estimated to be <50 femtograms (5x10^{-8} µg) per 0.5mL dose)
- For egg allergic persons, ACIP recs treat ccIIV same as egg-based IIVs
Recombinant Influenza Vaccine (RIV3)

- FluBlok® (Protein Sciences)
- Approved for persons aged 18 years and over
- Currently available only in trivalent formulation
- Considered egg-free
- Vaccine contains recombinant influenza virus HA
  - HA produced via introduction of the gene sequence into an insect cell line (Fall Armyworm) using a baculovirus vector
  - Contains 45 mcg HA derived from each vaccine virus (135 mcg total)
- Per ACIP recs, is an option for persons with egg allergy of any severity (for those within the indicated age range)
Live Attenuated Influenza Vaccine (LAIV4)

- FluMist® (MedImmune)
- Administered intranasally
- Quadrivalent only since 2013-14
- Approved for persons aged 2 through 49 years
  - ACIP recommends only for certain populations
Currently Available Influenza Vaccines (N=11)

- For many people, more than one option—examples:
  - Healthy 2 through 49 year olds—LAIV or IIV?
  - 65 years and older—standard dose or high dose IIV?
  - Pretty much anyone—quadrivalent or trivalent?

- ACIP makes no preferential recommendations for one product over another in situations where more than one is appropriate for a given individual
Determining Doses Needed for Children 6 months through 8 Years of Age

- Since 2010, counted doses of A(H1N1)pdm09 (2009 pandemic virus) separately
- For 2015-16, not counting separately doses of vaccine containing A(H1N1)pdm09
- If child in this age group has received ≥2 doses trivalent or quadrivalent influenza vaccine before July 2015, needs only one dose of 2015-16 vaccine
  - The 2 doses do not need to be from same or consecutive seasons

*The two doses need not have been received during the same season or consecutive seasons.
†Doses should be administered ≥4 weeks apart.

FIGURE 1. Influenza vaccine dosing algorithm for children aged 6 months through 8 years — Advisory Committee on Immunization Practices, United States, 2015–16 influenza season

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MMWR (2015) 64;30: 618-625
Persons for Whom LAIV Should Not Be Used (1)

LAIV should not be used in the following populations:

- Persons aged <2 years or >49 years;
- Those with contraindications listed in the package insert:
  - Children and adolescents receiving aspirin or aspirin-containing products;
  - Persons who have experienced severe allergic reactions to the vaccine or any of its components, or to a previous dose of any influenza vaccine;
- Pregnant women;
- Immunosuppressed persons;
- Persons with a history of egg allergy;
- Children aged 2 through 4 years who have asthma or who have had a wheezing episode noted in the medical record within the past 12 months, or for whom parents report that a health care provider stated that they had wheezing or asthma within the last 12 months;

MMWR (2014) 63;32: 691-697
Persons for Whom LAIV Should Not Be Used (2)

In addition to those on the previous slide, LAIV should not be used in the following populations (continued):

- Persons who have taken influenza antiviral medications within the previous 48 hours.

- Persons who care for severely immunosuppressed persons who require a protective environment should not receive LAIV, or should avoid contact with such persons for 7 days after receipt.

MMWR (2014) 63;32: 691-697
Precautions for the Use of LAIV

In addition to groups for whom LAIV is not recommended, the following are precautions for use of LAIV:

- Medical conditions that predispose to high risk of complications due to influenza (labeled precaution per the package insert);
- Asthma in persons aged ≥5 years (package insert notes potential increased risk of wheezing).
- Guillain-Barré Syndrome within 6 weeks of a prior dose of influenza vaccine (a precaution for all influenza vaccines)
- Moderate to severe illness with or without fever (a precaution for all influenza vaccines)
Influenza Antiviral Drugs: 2015-16

- Neuraminidase inhibitors (NAIs): oseltamivir (Tamiflu), zanamivir (Relenza), peramivir (Rapivab)
  - For treatment and prevention of influenza A and B
  - >99% of all circulating viruses were susceptible to NAIs during 2014-15
  - *Are recommended* for use during this season

- Investigational drug available: IV zanamivir

- Adamantanes: rimantadine and amantadine
  - High levels of resistance
  - *Not recommended* for use during this season
CDC Antiviral Recommendations

- All patients in the following categories with suspected or confirmed influenza should be treated as soon as possible, without waiting for confirmatory influenza testing
  - Hospitalized patients
  - Patients with severe, complicated, or progressive illness
  - Patients at high risk for complications from influenza (either outpatient or hospitalized)
Antiviral treatment may be prescribed on the basis of clinical judgment for any previously healthy (non-high risk) outpatient with suspected or confirmed influenza.
Persons at High Risk for Influenza Complications

- Children <2 years
- Adults >65 years
- Pregnant and postpartum (2 weeks after delivery)
- American Indians and Alaska Natives
- Persons who are morbidly obese (BMI ≥40)
- Residents of long-term care facilities
Persons at High Risk for Influenza Complications (continued)

- Persons with immunosuppression
- Persons <19 years who are receiving long-term aspirin therapy
- Persons with underlying medical conditions: chronic pulmonary, cardiovascular (except hypertension alone), renal, hepatic, hematologic, and metabolic disorders (incl. diabetes), or neurologic and neurodevelopment conditions
Influenza Antiviral Medications: The Data Behind the Recommendations

Clinical trials and observational data show that early antiviral treatment can:

- Shorten the duration of fever and illness symptoms
- Reduce the risk of complications (such as otitis media in children and pneumonia requiring antibiotics in adults)
- Reduce the risk of death among hospitalized patients
Efficacy of Neuraminidase Inhibitors: Uncomplicated influenza

Uncomplicated influenza (ambulatory patients)

- Reduces duration of influenza symptoms by average of 1-1.5 days when administered within 2 days of illness onset based on randomized placebo-controlled clinical trials (RCTs)

  - Reduces shedding by 20-30% each day, compared to placebo

  - Persons treated develop immunity
Thank You!

For more information please contact Centers for Disease Control and Prevention

1600 Clifton Road NE, Atlanta, GA 30333
Telephone, 1-800-CDC-INFO (232-4636)/TTY: 1-888-232-6348
E-mail: cdcinfo@cdc.gov Web: www.cdc.gov