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**Influenza Vaccine for 2018-2019**

Routine annual vaccination against influenza A and B viruses is recommended for everyone ≥6 months old. Recommendations for the current season for specific patient populations are listed in Tables 2 and 4.

**TIMING** — In the US, influenza vaccine should be offered by the end of October and continue to be offered as long as influenza is circulating in the community. In most adults, serum antibody levels peak about two weeks after vaccination.1

**COMPOSITION** — All seasonal influenza vaccines available in the US contain the same two influenza A virus antigens. Influenza A viruses are responsible for the majority of influenza-related morbidity and mortality, particularly in infants and older adults; influenza A(H3N2) has been associated with the highest rates of morbidity and mortality in older adults.2

Trivalent vaccines contain only one influenza B virus antigen (Victoria lineage). Quadrivalent vaccines contain influenza B virus antigens from both genetic lineages that have been circulating globally since the 1980s (Victoria and Yamagata), increasing the likelihood that the vaccine will provide protection against currently circulating strains.3,4 Influenza B viruses primarily infect children.2

**EFFECTIVENESS** — The effectiveness of seasonal influenza vaccine in preventing laboratory-confirmed influenza illness depends mainly on the match between the vaccine and circulating strains (type/subtype and antigenic similarity) and the immunologic response of the recipient. Vaccine effectiveness is greatest when the match is close, but even when it is

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**Table 1. 2018-2019 Influenza Vaccine Composition**

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>A/Michigan/45/2015 (H1N1)pdm09-like</td>
<td>A/Hong Kong/4801/2014 H3N2-like strain replaced the A/Hong Kong/4801/2014 H3N2-like strain in the 2017-2018 formulation and the B/Colorado/06/2017-like (Victoria lineage) strain in the 2017-2018 formulation. The other antigens are the same as those in last year's vaccine.</td>
</tr>
<tr>
<td>A/Singapore/INFIMH-16-0019/2016 (H3N2)-like</td>
<td>The A/Singapore/INFIMH-16-0019/2016 (H3N2)-like strain replaced the A/Singapore/INFIMH-16-0019/2016 (H3N2)-like strain in the 2017-2018 formulation. The other antigens are the same as those in last year's vaccine.</td>
</tr>
<tr>
<td>B/Colorado/06/2017-like (Victoria lineage)</td>
<td></td>
</tr>
<tr>
<td>B/Phuket/3073/2013-like (Yamagata lineage)</td>
<td></td>
</tr>
</tbody>
</table>

1. The A/Singapore/INFIMH-16-0019/2016 (H3N2)-like strain replaced the A/Hong Kong/4801/2014 H3N2-like strain in the 2017-2018 formulation and the B/Colorado/06/2017-like (Victoria lineage) strain in the 2017-2018 formulation. The other antigens are the same as those in last year's vaccine.
2. The live-attenuated vaccine (FluMist Quadrivalent) contains A/Slovenia/2903/2015 (an A/Michigan/45/2015 (H1N1)pdm09-like virus).

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**Table 2. Choice of Vaccine**

<table>
<thead>
<tr>
<th>Group</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children ≥6 months—&lt;2 years old</td>
<td>Age-appropriate inactivated vaccine (Afluria Quadrivalent, Fluvarix Quadrivalent, FluLaval Quadrivalent, or Fluzone Quadrivalent)</td>
</tr>
<tr>
<td>Adults 2-17 years old</td>
<td>Any age-appropriate inactivated or live-attenuated vaccine (Flublok Quadrivalent)</td>
</tr>
<tr>
<td>Adults ≥18 years old</td>
<td>Any age-appropriate inactivated or live-attenuated vaccine (Flublok Quadrivalent)</td>
</tr>
<tr>
<td>Pregnant women</td>
<td>Any age-appropriate inactivated or recombinant vaccine (Afluria Quadrivalent)</td>
</tr>
<tr>
<td>Persons with Egg Allergy</td>
<td>Any age-appropriate inactivated, recombinant, or live-attenuated vaccine (Flublok Quadrivalent)</td>
</tr>
<tr>
<td>Persons with Needle Aversion</td>
<td>Afluria or Afluria Quadrivalent with needle-free injector or intranasal live-attenuated vaccine (Flublok Quadrivalent)</td>
</tr>
<tr>
<td>Immunocompromised Persons</td>
<td>Any age-appropriate inactivated or recombinant vaccine (Afluria Quadrivalent)</td>
</tr>
</tbody>
</table>

1. See Table 4 for all available vaccines in the US during the 2018-19 influenza season and specific age recommendations.
2. Children 6 months to 8 years old who are being vaccinated for the first time or who have not received at least 2 lifetime doses of the trivalent or quadrivalent vaccine before July 1, 2018 should receive 2 doses at least 4 weeks apart. They should receive their first dose as soon as possible after the vaccine becomes available so that the second dose can be administered by the end of October. Children in this age group who received ≥2 doses of trivalent or quadrivalent vaccine at any time before July 1, 2018 require only 1 dose.
3. The Advisory Committee on Immunization Practices (ACIP) recommends the live-attenuated vaccine as an option this season. The American Academy of Pediatrics and the American Academy of Family Physicians recommend preferential use of an inactivated vaccine; they recommend the live-attenuated vaccine only for those who would otherwise not be vaccinated.
4. FDA-approved only for use in nonpregnant persons 2-49 years old. Not recommended for persons who are immunosuppressed, children 2-4 years old who have asthma or have had a wheezing episode in the previous 12 months, children or adolescents taking aspirin or salicylate-containing therapy, close contacts of severely immunosuppressed persons, or patients treated with influenza antiviral drugs in the previous 48 hours.
5. Fluid, Fluzone High-Dose, and Flublok Quadrivalent have elicited greater antibody responses in older adults than unadjuvanted standard-dose vaccines, but only the high-dose and recombinant vaccines have been shown to be more effective in preventing laboratory-confirmed influenza in randomized controlled trials (in adults ≥50 years old with the recombinant vaccine and in adults 65 years old with the high-dose vaccine). The ACIP has not made a preferential recommendation for any vaccine in this age group and states that vaccination should not be delayed if a specific product is not readily available.
6. A history of a severe allergic reaction to any component of the vaccine is a contraindication in the labeling of all influenza vaccines. However, the ACIP states that any age-appropriate inactivated influenza vaccine, recombinant influenza vaccine, or live-attenuated vaccine may be administered to persons with egg allergy of any severity. Persons who have severe egg allergy should be vaccinated in a healthcare setting. The recombinant vaccine (Flublok Quadrivalent) contains no egg proteins.
7. Delivery of Afluria or Afluria Quadrivalent using the PharmaJet Stratis needle-free injection system is FDA-approved only for persons 18-64 years old.
suboptimal, vaccination can still substantially reduce influenza-related hospitalization and death.5-9 (The vaccine strains selected for inclusion in the seasonal vaccine can mutate during production of egg-based vaccines, possibly resulting in a lower match between the vaccine and circulating strains.)

The interim adjusted overall effectiveness of the seasonal influenza vaccine in preventing laboratory-confirmed influenza for the 2017-18 season was 40%; effectiveness against group A viruses was 24% (H3N2) and 65% (H1N1) and against group B viruses was 49%.10

**LIVE-ATTENUATED VACCINE** — The intranasal live-attenuated influenza vaccine (Flumist Quadrivalent) is FDA-approved for healthy nonpregnant persons 2-49 years old (see Table 4, footnote 17 for contraindications). In recent seasons, there have been concerns about the efficacy of the live-attenuated vaccine against influenza A(H1N1)pdm09-like viruses, and the Advisory Committee on Immunization Practices (ACIP) advised against its use during the 2016-17 and 2017-18 seasons.11-13

This season the ACIP is once again recommending the live-attenuated influenza vaccine as an option. The 2018-19 quadrivalent live-attenuated vaccine contains a new A(H1N1)pdm09-like virus that was shed by a higher proportion of children after vaccination and induced significantly greater antibody responses than the previous live-attenuated vaccine, but clinical data demonstrating improved effectiveness are not yet available.14 The American Academy of Pediatrics and the American Academy of Family Physicians recommend use of the live-attenuated vaccine only for persons who would not otherwise be vaccinated.15,16

**OLDER ADULTS** — Older adults may have weaker immunogenic responses to influenza vaccination than younger adults, and their antibody levels may decline more rapidly.17,18 Recombinant, high-dose, and adjuvanted vaccines can improve antibody responses in these patients.

**Recombinant Vaccine** — Flublok Quadrivalent, a recombinant vaccine produced without the use of influenza virus or chicken eggs, contains three times the amount of antigen included in standard-dose vaccines and is FDA-approved for use in persons ≥18 years old. In adults 50-64 years old, the trivalent formulation of Flublok produced greater antibody responses to influenza A antigens than standard-dose trivalent vaccines.19 In a randomized, double-blind trial during the A/H3N2-predominant 2014-15 season, the recombinant quadrivalent vaccine was 30% more effective than a standard-dose unadjuvanted quadrivalent vaccine in preventing laboratory-confirmed influenza in adults ≥50 years old in a randomized controlled trial (42% more effective in those 50-64 years old and 17% more effective in those ≥65 years old).20

**Table 3. Vaccines for Older Adults**

<table>
<thead>
<tr>
<th>Vaccine Type</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recombinant Vaccine (Flublok Quadrivalent)</strong></td>
<td></td>
</tr>
<tr>
<td>Quadrivalent</td>
<td>Contains three times the amount of antigen included in standard-dose vaccines</td>
</tr>
<tr>
<td></td>
<td>Produced without use of influenza virus or eggs</td>
</tr>
<tr>
<td></td>
<td>FDA-approved for use in persons ≥18 years old</td>
</tr>
<tr>
<td></td>
<td>Induces greater antibody responses than unadjuvanted standard-dose vaccines in adults 50-64 years old</td>
</tr>
<tr>
<td></td>
<td>30% more effective than a standard-dose unadjuvanted quadrivalent vaccine in preventing laboratory-confirmed influenza in adults ≥50 years old in a randomized controlled trial (42% more effective in those 50-64 years old and 17% more effective in those ≥65 years old).</td>
</tr>
<tr>
<td><strong>High-Dose Vaccine (Fluzone High-Dose)</strong></td>
<td></td>
</tr>
<tr>
<td>Trivalent</td>
<td>Contains four times the amount of antigen included in standard-dose vaccines</td>
</tr>
<tr>
<td></td>
<td>FDA-approved for use in persons ≥65 years old</td>
</tr>
<tr>
<td></td>
<td>Induces greater antibody responses than unadjuvanted standard-dose vaccines in adults ≥65 years old</td>
</tr>
<tr>
<td></td>
<td>24% more effective than a standard-dose trivalent vaccine in preventing laboratory-confirmed influenza in adults ≥65 years old in a randomized controlled trial</td>
</tr>
<tr>
<td><strong>Adjuvanted Vaccine (Fluad)</strong></td>
<td></td>
</tr>
<tr>
<td>Trivalent</td>
<td>Contains MF59, an oil-in-water emulsion of squalene oil that increases the immune response</td>
</tr>
<tr>
<td></td>
<td>FDA-approved for use in persons ≥65 years old</td>
</tr>
<tr>
<td></td>
<td>Induces greater antibody responses than unadjuvanted standard-dose vaccines in adults ≥65 years old</td>
</tr>
<tr>
<td></td>
<td>In observational studies, adjuvanted vaccine recipients were less likely to develop influenza illness or be hospitalized for influenza or pneumonia than those who received an unadjuvanted standard-dose trivalent vaccine</td>
</tr>
</tbody>
</table>

1. No studies directly comparing these vaccines are available. The Advisory Committee on Immunization Practices (ACIP) has not made a preferential recommendation for any vaccine in older patients and states that vaccination should not be delayed if a specific product is not readily available.
dose influenza vaccine appeared to reduce the risk of respiratory-related death, compared to standard-dose vaccines. In a randomized trial in 172 solid-organ transplant recipients ≥18 years old, the high-dose vaccine induced significantly greater antibody responses than a standard-dose vaccine.25

### Adjuvanted Vaccine

The adjuvanted trivalent influenza vaccine (Fluad) is FDA-approved for use in persons ≥65 years old. It contains MF59, an oil-in-water emulsion of squalene oil that increases the immune response by recruiting antigen-presenting cells to the injection site and promoting uptake of influenza virus antigens. In a randomized trial in 7082 adults ≥65 years old, the adjuvanted vaccine elicited significantly greater antibody responses against all three influenza strains than the unadjuvanted trivalent vaccine, but the differences did not meet the prespecified criteria for superiority. In observational studies, older adults who received the adjuvanted trivalent influenza vaccine were less likely to develop symptomatic influenza illness or be hospitalized for influenza or pneumonia than those who received an unadjuvanted standard-dose trivalent vaccine.28,29

### CARDIOVASCULAR BENEFITS

In meta-analyses of randomized trials, influenza vaccination was associated with a reduced risk of major adverse cardiovascular events and death in patients at high risk for cardiovascular disease. The reduction in risk was greatest in those with a recent history of acute coronary syndrome.

### PREGNANCY

Vaccination of pregnant women not only protects them against influenza-associated illness, which can be especially severe during pregnancy.21

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### Table 4. Seasonal Influenza Vaccines for 2018-2019

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Available Formulations</th>
<th>Mercury Content</th>
<th>Recommended Age</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inactivated Trivalent (IIV3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Afluria (Seqirus)</td>
<td>0.5 mL syringe</td>
<td>none</td>
<td>≥6 months</td>
<td>$16.70</td>
</tr>
<tr>
<td>Fluad (Seqirus)</td>
<td>5 mL multidose vial</td>
<td>24.5 mcg/0.5 mL dose</td>
<td>≥6 months</td>
<td>15.40</td>
</tr>
<tr>
<td>Fluzone High-Dose (Sanofi Pasteur)</td>
<td>0.5 mL syringe</td>
<td>none</td>
<td>≥65 years</td>
<td>47.30</td>
</tr>
<tr>
<td>Inactivated Quadrivalent (IIV4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Afluria Quadrivalent (Seqirus)</td>
<td>0.5 mL syringe</td>
<td>none</td>
<td>≥6 months</td>
<td>17.20</td>
</tr>
<tr>
<td>Flurix Quadrivalent (GSK)</td>
<td>0.5 mL syringe</td>
<td>none</td>
<td>≥6 months</td>
<td>16.10</td>
</tr>
<tr>
<td>Fluad (Seqirus)</td>
<td>0.5 mL syringe</td>
<td>none</td>
<td>≥4 years</td>
<td>20.50</td>
</tr>
<tr>
<td>FluLaval Quadrivalent (GSK)</td>
<td>5 mL multidose vial</td>
<td>25 mcg/0.5 mL dose</td>
<td>≥4 years</td>
<td>19.40</td>
</tr>
<tr>
<td>Fluzone Quadrivalent (Sanofi Pasteur)</td>
<td>5 mL multidose vial</td>
<td>&lt;25 mcg/0.5 mL dose</td>
<td>≥6 months</td>
<td>15.00</td>
</tr>
<tr>
<td>Recombinant Inactivated Quadrivalent (RIIV4)</td>
<td>5 mL multidose vial</td>
<td>25 mcg/0.5 mL dose</td>
<td>≥6 months</td>
<td>15.90</td>
</tr>
<tr>
<td>Flumist Quadrivalent (AstraZeneca)</td>
<td>0.2 mL intranasal sprayer</td>
<td>none</td>
<td>≥18 years</td>
<td>46.20</td>
</tr>
<tr>
<td>Live-Attenuated Quadrivalent (LAIV4)</td>
<td>0.2 mL intranasal sprayer</td>
<td>none</td>
<td>2-49 years</td>
<td>23.00</td>
</tr>
</tbody>
</table>

2. Accumulating evidence shows no increased risk to vaccines containing mercury.
3. Children 6 months to 2 years old who are being vaccinated for the first time or who have not received at least 2 lifetime doses of the trivalent or quadrivalent vaccine before July 1, 2018 should receive 2 doses at least 4 weeks apart. They should receive their first dose as soon as possible after the vaccine becomes available, so that the second dose can be administered by the end of October. Children in this age group who received >2 doses of trivalent or quadrivalent vaccine at any time before July 1, 2018 require only 1 dose.
4. Approximate WAC per dose. WAC = wholesaler acquisition cost or manufacturer’s published price to wholesalers; WAC represents a published catalogue or list price and may not represent an actual transactional price.
5. Prepared by propagation of virus in embryonated eggs.
6. May contain residual amounts of neomycin sulfate and polymyxin B.
7. Patients 18-64 years old can receive the vaccine via a needle and syringe or a needle-free jet injector (PharmaJet Stratis).
8. Fluad is a standard-dose adjuvanted vaccine that contains MF59, an oil-in-water emulsion of squalene oil.
9. May contain residual amounts of neomycin and kanamycin.
10. Contains 50 mcg of hemagglutinin antigen from each strain, compared to 15 mcg in standard-dose vaccines.
11. May contain residual amounts of gentamicin sulfate.
13. The dose for children 6-35 months old is 0.25 mL and for those ≥3 years old is 0.5 mL.
14. Contains 45 mcg of hemagglutinin antigen from each strain, compared to 15 mcg in standard-dose vaccines. Contains no egg proteins.
15. Each 0.2 mL dose contains 10^6-10^7 FFU (fluorescent focus units) of live-attenuated influenza virus reassortants from each strain.
16. Each single-use sprayer contains a single 0.2-mL dose given intranasally (0.1 mL in each nostril). If nasal congestion that could impair vaccine delivery to the nasal mucosa is present, an injectable vaccine should be selected instead. If use of an injectable vaccine is unacceptable, influenza vaccination should be delayed.
17. Not recommended for pregnant women, persons who are immunosuppressed, children 2-4 years old who have asthma or have had a wheezing episode in the previous 12 months, children or adolescents taking aspirin or salicylate-containing therapy, close contacts of severely immunosuppressed persons, or patients treated with influenza antiviral drugs in the previous 48 hours.
pregnancy, but also protects their infants for up to the first 6 months of life.32-34

Most studies have not found an association between influenza vaccination and adverse pregnancy outcomes, but data demonstrating the safety of vaccination during the first trimester are limited. In one case-control study of 485 cases of spontaneous abortion (gestational age 5 to <20 weeks) that occurred during the 2010-11 and 2011-12 influenza seasons, administration of an inactivated influenza vaccine containing H1N1pdm09 was associated with an increased risk of miscarriage in the 28 days after vaccination among women who had received an H1N1pdm09-containing vaccine during the previous season35; a causal relationship has not been established.1 The ACIP and the American College of Obstetricians and Gynecologists continue to recommend influenza vaccination in pregnant women without regard to the trimester of pregnancy.36,37 The live-attenuated vaccine should not be used in pregnant women.

ADVERSE EFFECTS — Influenza vaccination has been associated with Guillain-Barré syndrome, but the absolute risk is very low, and influenza infection itself has also been associated with the syndrome.38,39

Except for soreness at the injection site, adverse reactions to inactivated influenza vaccines are uncommon. In clinical trials, Fluzone High-Dose caused more injection-site reactions than standard-dose influenza vaccines. Delivery of Afluria by needle-free jet injector has resulted in more mild to moderate local reactions than delivery by standard needle and syringe. Pain and tenderness at the injection site occurred more frequently with Fluad than with an unadjuvanted vaccine.

The most common adverse reactions associated with the live-attenuated vaccine are runny nose, nasal congestion, fever, and sore throat. The vaccine can increase the risk of wheezing, especially in children <5 years old with recurrent wheezing and in persons of any age with asthma. Persons vaccinated with the live-attenuated vaccine may shed the vaccine-strain virus for a few days after vaccination, but person-to-person transmission has been rare, and serious illness resulting from transmission has not been reported. Nevertheless, persons who care for severely immunocompromised patients in protected environments should not receive the live-attenuated vaccine or should avoid contact with such patients for 7 days after receiving it.

ALLERGY — A history of severe allergic reaction to any component of the influenza vaccine is a contraindication to vaccination. In 28 studies that included 4315 patients with egg allergy (656 with a history of a severe allergic reaction), there were no reports of anaphylaxis after administration of egg-based inactivated influenza vaccines; some mild reactions did occur.40 The ACIP, the American Academy of Allergy, Asthma and Immunology, and the American College of Allergy, Asthma and Immunology state that any age-appropriate influenza vaccine can be administered to persons who report a history of hives related to egg exposure. Persons with more severe egg allergy can also receive any age-appropriate influenza vaccine, but they should be vaccinated in a healthcare setting. The recombinant vaccine (Flublok Quadrivalent) contains no egg protein.

IMMUNOCOMPROMISED PERSONS — Immuno-compromised persons should not receive the live-attenuated influenza vaccine. Inactivated vaccines are generally considered safe for use in such persons, but the immune response may be reduced. Separation in time of influenza vaccination from an immunocompromising intervention might be considered.

WITH OTHER VACCINES — Inactivated and recombinant influenza vaccines can be administered concomitantly or sequentially with other inactivated or live vaccines. The live-attenuated influenza vaccine can be given simultaneously with inactivated or other live vaccines. Other live vaccines not administered on the same day should be given at least 4 weeks later. Because of the theoretical possibility of increased reactogenicity in patients receiving another adjuvanted vaccine (e.g., Shingrix), use of an unadjuvanted influenza vaccine might be considered in such patients.

CONCLUSION — Vaccination against seasonal influenza is recommended for all persons ≥6 months old, including pregnant women. Quadrivalent vaccines offer broader coverage against influenza B viruses, which primarily infect children. The intranasal live-attenuated vaccine is once again an ACIP-recommended option for the 2018-19 season. Recombinant, high-dose, and adjuvanted vaccines elicit greater antibody responses than standard-dose unadjuvanted vaccines in persons ≥65 years old, and the high-dose and recombinant vaccines have been shown in randomized controlled trials to be more effective in older patients in preventing laboratory-confirmed influenza.


