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Influenza Vaccine for 2020-2021

Annual vaccination against influenza A and B viruses is recommended for everyone ≥6 months old without a contraindication.1 Vaccination of all eligible persons can reduce the prevalence of influenza illness and symptoms that might be confused with those of COVID-19. Available vaccines and recommendations for specific patient populations for the 2020-2021 season are listed in Tables 2 and 3. Lower rates of influenza illness have been observed this season in the Southern Hemisphere, probably because of masking, social distancing, school closures, and travel restrictions.2

TIMING — In the US, vaccination against influenza should be offered by the end of October and should 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. Early vaccination (i.e., in July or August) may result in suboptimal immunity before the end of the influenza season, especially in older adults. Children who require 2 doses (see Table 3, footnote 2) should receive the first dose as early as possible so that the second dose can be given by the end of October. Vaccination should be postponed for persons with suspected or laboratory-confirmed COVID-19 infection, regardless of symptoms, until they are no longer acutely ill and no longer require isolation.

COMPOSITION — Influenza A viruses are the main cause of influenza-related morbidity and mortality, particularly in infants and older adults. Children are more likely than adults to become infected with influenza B.3

All seasonal influenza vaccines available in the US contain two influenza A virus antigens (see Table 1). Trivalent vaccines contain only one influenza B virus antigen; Fluar, an adjuvanted inactivated vaccine, is the only trivalent influenza vaccine available in the US this season. Quadrivalent vaccines contain influenza B virus antigens from both genetic lineages that have been circulating globally since the 1980s, increasing the likelihood that the vaccine will provide protection against currently circulating strains.4,5 The selected antigens may be altered during production of egg-based vaccines, possibly resulting in a less desirable match between the vaccine and circulating strains.

EFFECTIVENESS — Influenza vaccination reduces the incidence of laboratory-confirmed influenza and can reduce the risk of serious complications and death associated with influenza illness in children and adults.6-9 The effectiveness of the seasonal influenza vaccine in preventing laboratory-confirmed influenza illness depends on several factors, including the match between the vaccine and circulating strains and the immunologic response of the recipient. Vaccine effectiveness is greatest when the match is close, but even when it is suboptimal, vaccination can still substantially reduce the risk of influenza-related hospitalization and death.10-12

The interim adjusted overall effectiveness of the influenza vaccine in preventing laboratory-confirmed influenza infection during the 2019-2020 season was 45% (55% in children 6 months-17 years old). Effectiveness was 50% against influenza B viruses and 37% against influenza A(H1N1).13 In one observational cohort study, an increase in vaccination rates among preschool and elementary school children was associated with lower rates of hospitalization for influenza in older children and adults ≥65 years old.14

Table 1. 2020-2021 Influenza Vaccine Composition

<table>
<thead>
<tr>
<th>Trivalent Egg-Based Vaccine</th>
<th>Quadrivalent Egg-Based Vaccines</th>
<th>Quadrivalent Cell Culture-Based or Recombinant Vaccines</th>
</tr>
</thead>
<tbody>
<tr>
<td>A/Guangdong-Maonan/SWL1536/2019 (H1N1)pdm09-like</td>
<td>A/Hong Kong/2671/2019 (H3N2)-like</td>
<td>A/Hawaii/70/2019 (H1N1)pdm09-like</td>
</tr>
<tr>
<td>A/Hong Kong/2671/2019 (H3N2)-like</td>
<td>B/Washington/02/2019 (Victoria lineage)-like</td>
<td>A/Hong Kong/45/2019 (H3N2)-like</td>
</tr>
<tr>
<td>B/Washington/02/2019 (Victoria lineage)-like</td>
<td></td>
<td>B/Washington/02/2019 (Victoria lineage)-like</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B/Phuket/3073/2013 (Yamagata lineage)-like</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Antigenically similar to the A/Guangdong-Maonan/SWL1536/2019 (H1N1) pdm09-like virus in the egg-based vaccine.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
LIVE-ATTENUATED VACCINE — *FluMist Quadrivalent*, the intranasal live-attenuated influenza vaccine, is FDA-approved for use in healthy pregnant persons 2-49 years old (see Table 2, footnote 18 for contraindications). The Advisory Committee on Immunization Practices (ACIP) and the American Academy of Pediatrics (AAP) recommend the live-attenuated vaccine as an option this season.1,11 It was not a recommended option during the 2016-2017 and 2017-2018 seasons because of concerns about its efficacy against influenza A(H1N1)pdm09-like viruses.16-18 It was a recommended option for the 2018-2019 and 2019-2020 seasons based on changes in the A(H1N1)pdm09-like strain.

OLDER ADULTS — Older adults may have weaker immunogenic responses to influenza vaccination than younger adults, and their antibody levels may decline more rapidly, increasing vaccine effectiveness.19,20 Recombinant, high-dose, and adjuvanted vaccines can improve antibody responses in older patients, but whether they reduce the risk of hospitalization

### Table 2. Seasonal Influenza Vaccines for 2020-2021

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Available Formulations1</th>
<th>Mercury Content2</th>
<th>Recommended Age3</th>
<th>Cost4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inactivated Trivalent (IIV3)</td>
<td>0.5 mL syringe</td>
<td>none</td>
<td>≥65 years</td>
<td>$51.60</td>
</tr>
<tr>
<td>Flulavol Quadrivalent (Seqirus)5,7 0.5 mL syringe</td>
<td>none</td>
<td>6-35 months</td>
<td>17.90</td>
<td></td>
</tr>
<tr>
<td>Fluarix Quadrivalent (GSK)8,11 0.5 mL syringe</td>
<td>none</td>
<td>≥6 months</td>
<td>16.60</td>
<td></td>
</tr>
<tr>
<td>FluLaval Quadrivalent (GSK)9 0.5 mL syringe</td>
<td>none</td>
<td>≥6 months</td>
<td>16.60</td>
<td></td>
</tr>
<tr>
<td>Fluzone Quadrivalent (Sanofi Pasteur)10,12 0.5 mL syringe</td>
<td>none</td>
<td>≥6 months</td>
<td>14.00</td>
<td></td>
</tr>
<tr>
<td>Cell Culture-Based Inactivated Quadrivalent (ccIV4)</td>
<td>0.7 mL syringe</td>
<td>none</td>
<td>≥65 years</td>
<td>52.90</td>
</tr>
<tr>
<td>Flucelvax Quadrivalent (Seqirus)15 0.5 mL syringe</td>
<td>none</td>
<td>≥4 years</td>
<td>25.00</td>
<td></td>
</tr>
<tr>
<td>Recombinant Quadrivalent (RIV4)</td>
<td>0.5 mL syringe</td>
<td>none</td>
<td>2-49 years</td>
<td>23.00</td>
</tr>
<tr>
<td>Flublok Quadrivalent (Sanofi Pasteur)16,17 0.5 mL syringe</td>
<td>none</td>
<td>≥18 years</td>
<td>52.90</td>
<td></td>
</tr>
<tr>
<td>Live-Attenuated Quadrivalent (LAIV4)</td>
<td>0.2 mL intranasal sprayer19</td>
<td>none</td>
<td>2-49 years</td>
<td>23.00</td>
</tr>
</tbody>
</table>

2. Strong evidence shows no increased risk from exposure to vaccines containing mercury.
3. Children 6 months to 8 years old who are being vaccinated for the first time, whose vaccination history is not known, or who have not received at least 2 lifetime doses of the trivalent or quadrivalent vaccine before July 1, 2020 should receive 2 doses at least 4 weeks apart. The first dose should be given 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, 2020 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. Source: AnalySource® Monthly. September 5, 2020. Reprinted with permission by First Databank, Inc. All rights reserved. ©2020. www.fdbhealth.com/policies/drug-pricing-policy.
5. Prepared by propagation of virus in embryonated hen’s eggs.
7. May contain residual amounts of neomycin, kanamycin, and hydrocortisone.
8. May contain residual amounts of neomycin sulfate, polymyxin B, and hydrocortisone.
9. The dose for children 6–35 months old is 0.25 mL and for those ≥3 years old is 0.5 mL.
10. Persons 18-64 years old can receive the vaccine via a needle and syringe or a needle-free jet injector (PharmaJet Stratis).
11. May contain residual amounts of gentamicin sulfate and hydrocortisone.
12. The 0.25-mL prefilled syringe is not expected to be available for the 2020-2021 influenza season.
13. An injectable vaccine should be selected instead. If use of an injectable vaccine is unacceptable, influenza vaccination should be delayed.
14. Contraindicated for use in pregnant women, persons who are immunocompromised, persons with active communication between the CSF and oropharynx.
15. May contain residual amounts of gentamicin sulfate and hydrocortisone.
16. Use of influenza antiviral drugs could inhibit replication of the vaccine virus, reducing the vaccine’s efficacy. Some medical conditions (e.g., renal impairment) may require a longer interval between the antiviral drug regimen and administration of *FluMist Quadrivalent*. Patients of any age with asthma may be at increased risk of wheezing after administration of *FluMist Quadrivalent*.
17. Each single-use sprayer delivers one 0.2-mL intranasal dose (given as 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. Use of an injectable vaccine is unacceptable, influenza vaccination should be delayed.
The amount of antigen included in standard-dose influenza virus or chicken eggs, contains 3 times the recombinant vaccine produced without the use of 4.

Table 3. Choice of Vaccine

| Children 6 months–2 years old | Age-appropriate inactivated vaccine (Afluria Quadrivalent, Fluarix Quadvirant, FluvLaval Quadrivalent, or Fluzone Quadrivalent) |
| Adults <50 years old | Any age-appropriate inactivated or live-attenuated vaccine |
| Adults ≥50 years old | Any age-appropriate inactivated or recombinant vaccine |
| Pregnant Women | Any age-appropriate inactivated or recombinant vaccine |
| Persons with Egg Allergy | Afluria Quadrivalent with needle-free injector or intranasal live-attenuated vaccine |
| Persons with Needle Aversion | ACIP > Advisory Committee on Immunization Practices |
| Immunocompromised Persons | Any age-appropriate inactivated or recombinant vaccine |

and death remains to be established in randomized, controlled trials (see Table 4).21

Recombinant Vaccine — Flublok Quadrivalent, a recombinant vaccine produced without the use of influenza virus or chicken eggs, contains 3 times the amount of antigen included in standard-dose influenza vaccines. It is FDA-approved for use in persons ≥18 years old. In adults 50–64 years old, a recombinant trivalent vaccine used before approval of Flublok Quadrivalent produced greater antibody responses to influenza A antigens than a nonadjuvanted standard-dose inactivated trivalent vaccine.22

In a randomized, double-blind trial during the A/H3N2-predominant 2014–2015 season, the recombinant quadrivalent vaccine was 30% more effective than a nonadjuvanted standard-dose inactivated quadrivalent vaccine in preventing laboratory-confirmed influenza illness in 8604 adults ≥50 years old (42% more effective in persons 50–64 years old and 17% more effective in those ≥65 years old).23

High-Dose Vaccine — Fluzone High-Dose, an inactivated quadrivalent vaccine (last season’s high-dose vaccine was trivalent) that contains 4 times the amount of antigen included in standard-dose influenza vaccines, is FDA-approved for use in persons ≥65 years old. No published efficacy trials of the high-dose quadrivalent vaccine are available, but it offers broader protection than last year’s high-dose trivalent vaccine because of the added B strain.24,25 In a randomized, double-blind trial in 31,989 adults ≥65 years old during two influenza seasons, the high-dose trivalent vaccine induced significantly greater antibody responses than a standard-dose inactivated trivalent vaccine, and was 24.2% more effective in preventing laboratory-confirmed influenza illness.26 In observational studies and one meta-analysis in adults ≥65 years old, the high-dose trivalent vaccine was associated with a reduced risk of respiratory-related and all-cause hospitalization and death compared to standard-dose trivalent vaccines.27–30 In a retrospective cohort study, use of the high-dose trivalent vaccine during the 2016–2017 and 2017–2018 influenza seasons was associated with fewer respiratory hospitalizations than use of the adjuvanted trivalent vaccine.31

Adjuvanted Vaccine — The adjuvanted inactivated influenza vaccines Fluid and Fluarix Quadrivalent are FDA-approved for use in persons ≥65 years old.32 They contain 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 trivalent vaccine elicited significantly greater antibody responses against all three influenza strains than a nonadjuvanted trivalent vaccine, but the prespecified criteria for superiority were not met.33 In observational studies, older adults who received the
adjuvanted trivalent vaccine were less likely than those who received a nonadjuvanted standard-dose trivalent vaccine to develop symptomatic influenza illness or to be hospitalized for influenza or pneumonia.\(^3\) Randomized controlled trials demonstrating the efficacy of the adjuvanted vaccines in preventing laboratory-confirmed influenza in older adults are lacking.

**PREGNANCY** — The ACIP and the American College of Obstetricians and Gynecologists recommend that pregnant women be vaccinated against influenza without regard to the trimester of pregnancy,\(^36,37\) but they should not receive the live-attenuated vaccine. Vaccination protects pregnant women against influenza-associated illness, which can be especially severe during pregnancy, and protects their infants for up to the first 6 months after birth.\(^38-40\)

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.

**ALLERGY** — A history of a severe allergic reaction to any component of the influenza vaccine is listed as a contraindication in the labeling of all influenza vaccines. 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.\(^41\) 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 those who receive egg-based vaccines should be vaccinated in a healthcare setting with supervision by a healthcare provider experienced in recognizing and managing severe allergic reactions. The recombinant vaccine (Flublok Quadrivalent) and the cell culture-based inactivated vaccine (Flucelvax Quadrivalent) are not prepared by propagation of virus in embryonated eggs.

**IMMUNOCOMPROMISED PERSONS** — The live-attenuated influenza vaccine should not be used in immunocompromised persons. Inactivated and recombinant 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.

In solid-organ transplant recipients ≥18 years old, the high-dose vaccine induced significantly greater antibody and cellular responses than standard-dose vaccines.\(^42,43\) In a randomized trial in 279 patients with rheumatoid arthritis treated with various immunosuppressive drugs, immune responses to the influenza vaccine were higher in patients given a high-dose vaccine than in those given a standard-dose vaccine.\(^44\)

**ADVERSE EFFECTS** — Influenza vaccination has been associated with Guillain-Barré syndrome, but the absolute risk is very low (about 1-2 additional cases
per million persons vaccinated). Influenza infection itself has been associated with the syndrome (about 17 cases per million influenza infection encounters).45,46

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

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 who receive 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.

USE WITH OTHER VACCINES — Inactivated and recombinant influenza vaccines can be administered concomitantly or sequentially with live or other inactivated vaccines. The live-attenuated influenza vaccine can be given simultaneously with inactivated or other live vaccines. Other live vaccines not administered simultaneously should be given at least 4 weeks later. Use of a nonadjuvanted influenza vaccine could be considered in persons receiving an adjuvanted vaccine (e.g., Shingrix, Heplisav-B); coadministration of Shingrix and a nonadjuvanted inactivated quadrivalent vaccine has not been associated with decreased immunogenicity to either vaccine.47

USE WITH INFLUENZA ANTIVIRALS — Use of oseltamivir or zanamivir within 48 hours before, peramivir within 5 days before, or baloxavir marboxil within 17 days before or <2 weeks after administration of the intranasal live-attenuated influenza vaccine could inhibit replication of the vaccine virus, reducing the vaccine’s efficacy.

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. The intranasal live-attenuated vaccine is a recommended option for the 2020–2021 season. Recombinant, high-dose, and adjuvanted vaccines elicit greater antibody responses than nonadjuvanted standard-dose vaccines in persons ≥65 years old, and randomized controlled trials have shown that the high-dose and recombinant vaccines are more effective for prevention of laboratory-confirmed influenza in older persons.47
47. TF Schwarz et al. Immunogenicity and safety of an adjuvanted herpes zoster subunit vaccine coadministered with seasonal influenza vaccine in adults aged 50 years or older. J Infect Dis 2017; 216:1352.