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## on Drugs and Therapeutics

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# The Medical Letter®

## on Drugs and Therapeutics

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### ▶ Influenza Vaccine for 2023-2024

Annual vaccination in the US against influenza A and B viruses is recommended for everyone  $\geq 6$  months old without a contraindication.<sup>1,2</sup> Influenza vaccines that are available in the US for the 2023-2024 season are listed in Table 2.

**COMPOSITION** – All influenza vaccines available in the US this season are quadrivalent; they contain two influenza A and two influenza B virus antigens (see Table 1). Influenza A viruses are the main cause of influenza-related morbidity and mortality, especially in older adults. Illness caused by influenza B viruses is usually more severe in children, especially in those  $< 5$  years old.<sup>3</sup>

Table 1. 2023-2024 Influenza Vaccine Composition<sup>1</sup>

#### Egg-Based Vaccines

A/Victoria/4897/2022 (H1N1)pdm09-like  
A/Darwin/9/2021 (H3N2)-like  
B/Austria/1359417/2021 (Victoria lineage)-like  
B/Phuket/3073/2013 (Yamagata lineage)-like

#### Cell Culture-Based and Recombinant Vaccines

A/Wisconsin/67/2022 (H1N1)pdm09-like  
A/Darwin/6/2021 (H3N2)-like  
B/Austria/1359417/2021 (Victoria lineage)-like  
B/Phuket/3073/2013 (Yamagata lineage)-like

1. All influenza vaccines available in the US for the 2023-2024 influenza season are quadrivalent.

**TIMING** – In the US, vaccination against influenza should ideally be offered in September or October and continue to be offered as long as influenza viruses are circulating in the community. In most adults, serum antibody levels peak 1-2 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 adults  $\geq 65$  years old.<sup>4</sup>

The Advisory Committee on Immunization Practices (ACIP) recommends that pregnant women who are in their first or second trimester during July or August wait until September or October to be vaccinated to ensure that their babies are protected throughout the influenza season, unless vaccination later is not possible; vaccination during July or August can be considered for women who are in their third trimester.<sup>1</sup>

#### Key Points: Influenza Vaccine for 2023-2024

- ▶ Annual vaccination against influenza A and B viruses is recommended for everyone in the US  $\geq 6$  months old without a contraindication.
- ▶ Vaccination should ideally be offered in September or October and continue to be offered as long as influenza viruses are circulating in the community.
- ▶ All influenza vaccines available in the US this season are quadrivalent; they contain two influenza A and two influenza B virus antigens.
- ▶ Influenza vaccination reduces the incidence of laboratory-confirmed influenza and the risk of serious complications and death associated with influenza illness.
- ▶ In adults  $\geq 65$  years old, use of a high-dose, adjuvanted, or recombinant vaccine can improve immune responses and is preferentially recommended over other influenza vaccines.
- ▶ Pregnant women should be vaccinated against influenza.
- ▶ The ACIP states that persons with a history of egg allergy can receive any age-appropriate influenza vaccine. Additional safety measures are no longer recommended for this patient population.

Children aged 6 months through 8 years who require 2 doses should receive the first dose as early as possible so that the second dose can be given by the end of October; children in this age group who previously received two doses of an influenza vaccine will only need one dose this season (see Table 2, footnote 3). Vaccination in September or October is preferred for children of any age who need only one dose, but administration in July or August can be considered.

Vaccination of persons with moderate or severe COVID-19 should be postponed until after recovery from acute illness.<sup>1</sup>

**EFFECTIVENESS** – Influenza vaccination reduces the incidence of laboratory-confirmed influenza and the risk of serious complications and death associated with influenza illness.<sup>5-8</sup> The effectiveness of the seasonal influenza vaccine in preventing 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.<sup>9-11</sup> During the current influenza season in the Southern Hemisphere,

vaccination was associated with a 52% reduction in the risk of influenza-associated hospitalizations.<sup>12</sup>

**OLDER ADULTS** – Older adults are at increased risk for severe influenza-associated illness, hospitalization, and death. They may have weaker immunogenic responses to influenza vaccination than younger persons, and their antibody levels may decline more rapidly, decreasing vaccine effectiveness.<sup>13</sup>

In a cohort study of hospitalized adults  $\geq 60$  years old with cardiovascular disease, influenza vaccination was associated with a reduced risk of in-hospital death, recurrent hospitalization for ischemic heart disease, and respiratory hospitalization during the influenza season.<sup>14</sup>

**High-Dose Vaccine** – *Fluzone High-Dose Quadrivalent*, an inactivated vaccine that contains 4 times the amount of antigen included in standard-dose inactivated influenza vaccines, is FDA-licensed for use in persons  $\geq 65$  years old.

In a randomized, double-blind trial in 31,989 adults  $\geq 65$  years old during 2 influenza seasons, a high-dose inactivated trivalent vaccine (*Fluzone High-Dose*; no longer available) induced significantly greater antibody responses than a standard-dose inactivated trivalent vaccine and was 24% more effective in preventing laboratory-confirmed influenza illness.<sup>15</sup> In observational studies and randomized trials in adults  $\geq 65$  years old, use of a high-dose inactivated trivalent or quadrivalent vaccine was associated with a reduced risk of respiratory-related and all-cause hospitalization and death compared to standard-dose inactivated trivalent or quadrivalent vaccines.<sup>16-20</sup>

In a randomized trial in 5260 patients (mean age 65.5 years) with high-risk cardiovascular disease, use of a high-dose inactivated trivalent vaccine over 3 influenza seasons did not significantly reduce all-cause mortality or cardiopulmonary hospitalizations compared to standard-dose inactivated quadrivalent vaccines.<sup>21</sup>

**Adjuvanted Vaccine** – *Fluad Quadrivalent*, an adjuvanted inactivated influenza vaccine, is FDA-licensed for use in persons  $\geq 65$  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  $\geq 65$  years old, an adjuvanted inactivated trivalent vaccine (*Fluad*; no longer available) elicited significantly greater

antibody responses than a nonadjuvanted, standard-dose inactivated trivalent vaccine.<sup>22</sup> In observational studies and randomized trials, older adults who received an adjuvanted inactivated trivalent vaccine were less likely to develop symptomatic influenza illness or be hospitalized for influenza or pneumonia than those who received a nonadjuvanted, standard-dose inactivated trivalent vaccine.<sup>23-25</sup>

**Recombinant Vaccine** – *Flublok Quadrivalent*, a recombinant influenza vaccine produced without use of influenza virus or chicken eggs, contains 3 times the amount of antigen included in standard-dose inactivated influenza vaccines. It is FDA-licensed for use in persons  $\geq 18$  years old.

In a retrospective cohort study in 12.7 million adults  $\geq 65$  years old vaccinated during the 2019-2020 influenza season, the recombinant quadrivalent vaccine was more effective in preventing hospital visits than a nonadjuvanted, standard-dose inactivated quadrivalent vaccine, an adjuvanted trivalent vaccine, and a high-dose trivalent vaccine.<sup>26</sup>

**Choice of Vaccine** – In a recent trial in community-dwelling adults 65-82 years old, high-dose, adjuvanted, and recombinant influenza vaccines improved humoral and cell-mediated immune responses compared to standard-dose inactivated vaccines.<sup>27</sup> Few trials have directly compared the high-dose, adjuvanted, and recombinant vaccines in older adults and none have shown that any one vaccine is superior to another.

The ACIP preferentially recommends use of a high-dose, adjuvanted, or recombinant influenza vaccine over other available age-appropriate influenza vaccines in adults  $\geq 65$  years old; if none of these vaccines are available, any age-appropriate influenza vaccine should be given.<sup>1</sup>

**PREGNANCY** – Vaccination protects pregnant women against influenza-associated illness, which can be especially severe during pregnancy, and protects their infants for up to 6 months after birth (influenza vaccines are not approved for use in infants  $< 6$  months old).<sup>28</sup>

The ACIP and the American College of Obstetricians and Gynecologists (ACOG) recommend that pregnant women be vaccinated against influenza (see Timing section on page 1).<sup>29,30</sup> Pregnant women can receive any age-appropriate inactivated or recombinant influenza vaccine; the live-attenuated intranasal vaccine (*FluMist Quadrivalent*) should not be used during pregnancy.

Table 2. Seasonal Influenza Vaccines for 2023-2024

Vaccine <sup>1</sup>	Available Formulations <sup>2</sup>	Recommended Age <sup>3</sup>	Cost <sup>4</sup>
<b>Standard-Dose Inactivated Quadrivalent (IIV4); egg-based</b>			
<i>Afluria Quadrivalent</i> (Seqirus) <sup>5,6</sup>	0.5 mL syringe	≥3 years	\$20.00
	5 mL multidose vial <sup>7</sup>	≥6 months <sup>8</sup>	18.50
<i>Fluarix Quadrivalent</i> (GSK) <sup>9</sup>	0.5 mL syringe	≥6 months	19.00
<i>FluLaval Quadrivalent</i> (GSK)	0.5 mL syringe	≥6 months	19.00
<i>Fluzone Quadrivalent</i> (Sanofi)	0.5 mL syringe, vial	≥6 months <sup>10</sup>	19.00
	5 mL multidose vial <sup>7</sup>	≥6 months <sup>10</sup>	17.70
<b>High-Dose Inactivated Quadrivalent (HD-IIV4); egg-based</b>			
<i>Fluzone High-Dose Quadrivalent</i> (Sanofi) <sup>11</sup>	0.7 mL syringe	≥65 years	63.80
<b>Standard-Dose, Adjuvanted Inactivated Quadrivalent (aIIV4); egg-based</b>			
<i>Fluad Quadrivalent</i> (Seqirus) <sup>12,13</sup>	0.5 mL syringe	≥65 years	67.20
<b>Standard-Dose, Cell Culture-Based Inactivated Quadrivalent (ccIIV4)</b>			
<i>Flucelvax Quadrivalent</i> (Seqirus) <sup>14</sup>	0.5 mL syringe	≥6 months	29.40
	5 mL multidose vial <sup>7</sup>	≥6 months <sup>15</sup>	27.80
<b>Recombinant Quadrivalent (RIV4)</b>			
<i>Flublok Quadrivalent</i> (Sanofi) <sup>16</sup>	0.5 mL syringe	≥18 years	63.80
<b>Live-Attenuated Quadrivalent (LAIV4); egg-based</b>			
<i>FluMist Quadrivalent</i> (AstraZeneca) <sup>9</sup>	0.2 mL intranasal sprayer <sup>17,18</sup>	2-49 years <sup>19</sup>	24.50

- All inactivated quadrivalent vaccines and the recombinant vaccine are given by IM injection. The live-attenuated quadrivalent vaccine is given intranasally.
- Single-dose vials and syringes are sold in boxes of 10. Multidose vials contain 10 doses.
- 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 a trivalent or quadrivalent influenza vaccine before July 1, 2023 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 given by the end of October. Children in this age group who received ≥2 doses of a trivalent or quadrivalent influenza vaccine at any time before July 1, 2023 require only 1 dose.
- 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, 2023. Reprinted with permission by First Databank, Inc. All rights reserved. ©2023. www.fdbhealth.com/policies/drug-pricing-policy.
- May contain residual amounts of neomycin sulfate, polymyxin B, and hydrocortisone.
- Delivery of *Afluria Quadrivalent* via the *PharmaJet Stratis* needle-free injection system is FDA-licensed for persons 18-64 years old.
- Contains ~25 mcg/0.5 mL dose of mercury; strong evidence shows no adverse outcomes related to exposure to vaccines containing mercury.
- The dose is 0.25 mL for children 6-35 months old and 0.5 mL for those ≥3 years old.
- May contain residual amounts of gentamicin sulfate.
- The dose is either 0.25 mL or 0.5 mL for children 6-35 months old and 0.5 mL for those ≥3 years old. The 0.25-mL prefilled syringes are no longer available; if a prefilled syringe is used in children 6-35 months old, the dose volume should be 0.5 mL.
- Contains 60 mcg of hemagglutinin antigen from each strain, compared to 15 mcg in standard-dose inactivated vaccines.
- Contains MF59, an oil-in-water emulsion of squalene oil.
- May contain residual amounts of neomycin, kanamycin, and hydrocortisone.
- Uses mammalian cells for replication rather than hen's eggs.
- The dose is 0.5 mL for children ≥6 months old.
- Contains 45 mcg of hemagglutinin antigen from each strain, compared to 15 mcg in standard-dose inactivated vaccines. Contains no egg proteins.
- Each 0.2-mL dose contains 10<sup>6.5</sup>-10<sup>7.5</sup> FFU (fluorescent focus units) of live-attenuated influenza virus reassortants from each strain.
- 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. If use of an injectable vaccine is unacceptable, influenza vaccination should be delayed.
- Per ACIP, contraindicated for use in patients with a severe allergic reaction to any component of the vaccine or to a previous dose of any influenza vaccine, pregnant women, persons who are immunocompromised, persons with active communication between the CSF and oropharynx, nasopharynx, nose, or ear or any other cranial CSF leak, persons with cochlear implants, children 2-4 years old who have asthma or have had a wheezing episode within the previous 12 months, persons without a spleen or with a nonfunctioning spleen, children or adolescents taking aspirin or salicylate-containing therapy, close contacts of severely immunocompromised persons who require a protected environment, or patients treated with oseltamivir or zanamivir within the previous 48 hours, peramivir within the previous 5 days, or baloxavir marboxil within the previous 17 days. Use of influenza antiviral drugs <2 weeks after administration of the intranasal live-attenuated vaccine could inhibit replication of the vaccine virus, reducing the vaccine's effectiveness. 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*.

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.<sup>31</sup> In one prospective study in women who were planning on becoming pregnant or who were pregnant, exposure to an influenza vaccine before or during pregnancy was not associated with an increased rate of miscarriage.<sup>32</sup>

**EGG ALLERGY** – The recombinant vaccine (*Flublok Quadrivalent*) and the cell culture-based inactivated vaccine (*Flucelvax Quadrivalent*) do not contain egg protein. Other available influenza vaccines may

contain trace amounts of egg protein (ovalbumin), but numerous studies have found that patients with a history of egg allergy are not at increased risk for a reaction to influenza vaccines that are propagated in eggs.<sup>33</sup>

The ACIP, the American Academy of Pediatrics (AAP), and the Joint Task Force on Practice Parameters of the American Academy of Allergy Asthma and Immunology and the American College of Allergy Asthma and Immunology state that persons with a history of egg allergy of any severity can receive any egg- or nonegg-based age-appropriate influenza vaccine without the need for additional safety measures.<sup>1,2,34</sup>

The American Academy of Pediatrics adds that it is not necessary to inquire about egg allergy before administration of any influenza vaccine, including on screening forms.<sup>2</sup>

**IMMUNOCOMPROMISED PERSONS** — The live-attenuated intranasal 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. In two randomized trials in solid-organ transplant recipients, the high-dose vaccine induced significantly greater immune responses than standard-dose vaccines.<sup>35,36</sup> Separating the time of influenza vaccination from that of an immunocompromising intervention might be considered.

**USE WITH OTHER VACCINES** — Any influenza vaccine can be given at the same time as a **COVID-19 vaccine**, but the vaccines should be administered in separate arms. The ACIP states that coadministration of a **respiratory syncytial virus (RSV)** vaccine with other adult vaccines during the same visit is acceptable; RSV and influenza antibody titer levels are somewhat lower with coadministration of a quadrivalent seasonal influenza vaccine and a RSV vaccine than with sequential administration (~1 month apart).<sup>37</sup>

**Inactivated** and **recombinant** influenza vaccines can be administered concomitantly or sequentially with live or other inactivated or recombinant vaccines. The **live-attenuated** intranasal 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. Because of limited safety data on concurrent use of 2 or more **adjuvanted** vaccines, use of a nonadjuvanted influenza vaccine may be considered when another adjuvanted vaccine (e.g., *Shingrix*, *Hepelisav-B*) is going to be administered concurrently.

**USE WITH INFLUENZA ANTIVIRALS** — Any inactivated or recombinant influenza vaccine can be administered to persons receiving antiviral drugs for treatment or chemoprophylaxis of influenza. Use of oseltamivir (*Tamiflu*, and generics) or zanamivir (*Relenza*) within 48 hours before, peramivir (*Rapivab*) within 5 days before, or baloxavir marboxil (*Xofluz*) within 17 days before administration of the live-attenuated intranasal influenza vaccine could inhibit replication of the vaccine virus, reducing the vaccine's effectiveness. Persons who receive any of these antiviral drugs during these specified times and through 2 weeks after administration of the live-

attenuated vaccine should be revaccinated with an inactivated or recombinant influenza vaccine.

**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), and influenza infection itself has been associated with the syndrome (about 17 cases per one million patients hospitalized with influenza).<sup>38</sup> In a prospective cohort study in patients with diabetes, influenza vaccination was associated with hyperglycemia, but serum glucose levels returned to baseline 2 days after vaccination.<sup>39</sup>

Except for soreness at the injection site, adverse reactions to **inactivated** influenza vaccines are uncommon. In clinical trials, a **high-dose** vaccine (*Fluzone High-Dose* trivalent) caused more injection-site reactions than standard-dose influenza vaccines. Pain and tenderness at the injection site also occurred more frequently with an **adjuvanted** vaccine (*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** intranasal vaccine are runny nose, nasal congestion, fever, and sore throat. The vaccine may increase the risk of wheezing, especially in children <5 years old with recurrent wheezing and in persons of any age with asthma. However, a recent study in 151 children with asthma found that the frequency of asthma exacerbations and asthma-related symptoms was similar with the live-attenuated influenza vaccine and a quadrivalent inactivated influenza vaccine.<sup>40</sup> 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, the ACIP states that 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.

**INVESTIGATIONAL VACCINES** — Vaccines that provide universal protection against all influenza strains are in development. A vaccine designed to protect against influenza, COVID-19, and respiratory syncytial virus, the three primary causes of viral respiratory disease in older adults, is in development. ■

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