THE PACKAGE INSERT SERIES

Flu Vaccines — What the Labels Say About the Shots Recommended Every Year

BY

Unbekoming

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unbekoming.com

In March 2026, the FDA-approved prescribing information for three of the most-administered seasonal flu vaccines in the United States — Afluria, Flucelvax and Fluzone — received a new warning. Section 5.4 was added to all three labels on the same date: Febrile Seizures. The warning is based on post-marketing observational studies from the 2023-2024 and 2024-2025 respiratory seasons, which found a 97% increase in relative risk for febrile seizures in the first day after standard-dose quadrivalent vaccination in children aged 6 months through 4 years, and a 194% increase after the trivalent. The Flucelvax label states the data "suggest a causal relationship". The warning did not exist a year ago. It was added one month before this installment.

> *Across the nine flu vaccine labels covered in this installment, the pattern is not about one product. Every label admits the vaccine has not been evaluated for carcinogenic or mutagenic potential, or for impairment of fertility. Every label states the vaccine "may not protect all recipients". Every label concedes that antibodies against one strain "confer limited or no protection" against another — which matters because the product is reformulated every year based on a strain guess made months before the season begins, and the current year's reformulation is not tested for efficacy before being administered. One adult product, Fluad Quadrivalent, has been on the market under accelerated approval since 2020 on condition that continued approval "may be contingent upon verification and description of clinical benefit in a confirmatory trial". The FluMist label reports that, in a daycare transmission study, at least one vaccine strain was isolated from 80% of FluMist recipients for a mean of 7.6 days, including one confirmed case of recovery in an unvaccinated daycare contact.*

These are statements from the FDA-approved labels, written by the manufacturers, reviewed by the regulators, and filed with the agency.

This installment covers nine products — the full US-licensed flu vaccine market for the 2025-2026 season: Fluzone and Fluzone High-Dose (Sanofi), Fluarix and Flulaval (GSK), Flucelvax, Fluad and Afluria (Seqirus), Flublok (Protein Sciences/Sanofi), and FluMist (MedImmune/AstraZeneca). The labels analysed span formulas from 2019 through 2025-2026. Beginning with the 2024-2025 season, the FDA transitioned all US flu vaccines from quadrivalent to trivalent formulations, dropping the B/Yamagata lineage after it had not been detected in circulation since March 2020 — a reformulation that was itself implemented without new efficacy or safety trials. Where the labels cited here describe quadrivalent products, the findings carry over to the current trivalent reformulations, which have not themselves been trial-tested before market release. Everything that follows is

drawn from the prescribing information for these products.

The Package Insert reads the FDA-approved labels for a major drug or vaccine class in each installment and reports what the documents actually say — including what they admit has not been studied. If you're currently considering a flu shot, have a child under 5, are pregnant, or are over 65, this is the installment to start with.

> A note on language
> This series reads what the FDA-approved prescribing information actually says, in the terms the labels themselves use. Those terms come from conventional pharmacology and immunology — antibodies, immune response, autoimmune, immunogenicity, and similar. I do not accept that vocabulary as a description of what the body is actually doing, and readers of my other work know the reasons.

I use the terms in these installments for a specific reason: the strongest critique of a pharmaceutical label is almost always the label's own words, measured by the label's own methods, admitted by the label's own manufacturer. Softening the terminology loses the force of the admission. When a label reports that 51% of patients developed antibodies and then admits it cannot characterise the effect of those antibodies, the reader should see both halves in the label's own language. The measurement and the admission belong together.

This installment engages with that vocabulary more heavily than most, because the flu vaccine labels rest on germ-theory assumptions — circulating viruses, strains, transmission, antigenic drift. I report what the labels say in the labels' own terms. Whether the framework producing the claims is the right framework is a separate question, discussed elsewhere.

The Warning Added Last Month

The Afluria, Flucelvax and Fluzone prescribing information all list the addition under “Recent Major Changes” at the top of the label: Warnings and Precautions, Febrile Seizures (5.4) 03/2026. The identical text appears in Section 6.2 of each label:

> *The association between influenza vaccine and febrile seizures was evaluated in children ages 6 months through 4 years during the 2023-2024 and 2024-2025 respiratory seasons using three commercial health insurance claims data sources. A self-controlled case series analysis compared the risk of febrile seizures within a risk window of 0 to 1 day postvaccination to a control window of 8 to 63 days postvaccination. The attributable risk from one data partner was reported as 21.2 per million excess febrile seizure episodes, corresponding to a 97% increase in relative risk* (IRR: 1.97, 95% CI:

> *1.09, 3.54) following standard-dose quadrivalent vaccine. For standard-dose trivalent vaccine, the figure was 44.2 per million excess episodes, corresponding to a 194% increase in relative risk* (IRR: 2.94, 95% CI: 1.72, 5.01).

The label concludes: The results of this type of observational study suggest a causal relationship between standard dose influenza quadrivalent and trivalent vaccines and febrile seizures in children 6 months through 4 years of age.

That three separate products from three separate manufacturers received the same new warning on the same date indicates this is not a product-specific finding. The excess risk was observed across the class of standard-dose inactivated influenza vaccines administered to children under 5.

The study compared risk in a specific two-day window after vaccination to the risk in a control period of day 8 through day 63 — meaning the comparison was within the same children, against themselves, at a later post-vaccination date. That design controls for everything about the child except the timing relative to the shot. The confidence intervals do not cross 1.0, which means the signal is statistically distinguishable from chance at the conventional threshold. The warning is now in the label, but the product remains on the ACIP schedule with no change to recommendations for the 6-month-to-4-year age group — the same group the label now identifies as at increased seizure risk within 24 hours of vaccination. Parents are not being given this new information at the time of administration. It appears in a document most parents never see.

ASK YOUR DOCTOR

Was I informed of the March 2026 febrile seizure warning before my child received a flu vaccine? If not, why not? How will I be able to distinguish a post-vaccine febrile seizure from any other seizure, and what should I do if it occurs?

What the Vaccines Are Approved to Do

The indications section of every flu vaccine label in this installment reads close to identically. Fluzone Quadrivalent: “indicated for active immunization for the prevention of disease caused by influenza A subtype viruses and type B viruses contained in the vaccine”. Fluarix: the same. Flulaval: the same. Flucelvax: the same. Flublok: “active immunization against disease caused by influenza A subtype viruses and influenza type B viruses contained in the vaccine”. FluMist: “active immunization for the prevention of influenza disease caused by influenza virus subtypes A and type B contained in the vaccine”.

Note what each indication specifies: prevention of disease caused by the specific strains contained in the vaccine. Not prevention of flu-like illness in general. Not prevention of

respiratory infection. Not reduction in mortality. Not reduction in hospitalisation. Not reduction in transmission. The approved indication is specific to the strains the manufacturer put in the vial for that season — four for the older quadrivalent products, three for the current trivalent reformulations.

For three of the nine products — Fluzone High-Dose, Flublok and Fluad — the approved indication was granted based on antibody levels rather than a fresh trial showing prevention of illness. The Afluria label, in its own mechanism of action section, carries a sentence that makes clear what this approval strategy rests on: “Specific levels of hemagglutination inhibition (HI) antibody titers post-vaccination with inactivated influenza vaccine have not been correlated with protection from influenza virus. In some human studies, antibody titers of 1:40 or greater have been associated with protection from influenza illness in up to 50% of subjects.” Antibody titres — the measure on which the surrogate approvals rest — have not been correlated with protection. The titres are associated with protection in half of subjects, not all, and only at particular thresholds in particular studies.

Fluzone High-Dose Quadrivalent was approved based on “immunologic non-inferiority” to its trivalent predecessor, measured by haemagglutinin-inhibition geometric mean titres and seroconversion rates. The Fluzone High-Dose label states plainly: “The efficacy of Fluzone High-Dose (trivalent formulation) is relevant to Fluzone High-Dose Quadrivalent since both vaccines are manufactured according to the same process and have overlapping compositions.” The quadrivalent product on the shelf has never had its own efficacy trial. The trivalent trial it inherits (Study 2, NCT01427309) showed a 24.2% relative efficacy versus standard Fluzone in adults 65 and older — meaning 1.43% of High-Dose recipients still developed laboratory-confirmed influenza, compared to 1.89% of standard-dose recipients. The absolute risk reduction was 0.46 percentage points.

Flublok Quadrivalent tells the same structural story. The label: “The efficacy of Flublok (trivalent formulation) is relevant to Flublok Quadrivalent because both vaccines are manufactured using the same process and have overlapping compositions.” When the trivalent Flublok ran its primary efficacy trial (Study 3, 2007-2008 season, 4,648 healthy adults), the outcome was unusual. The label: “Vaccine efficacy against antigenically matched culture-confirmed CDC-ILI could not be determined reliably because 96% of the influenza isolates obtained from subjects in Study 3 were not antigenically matched to the strains represented in the vaccine.” Ninety-six percent. The 44.8% efficacy figure the label ultimately reports is from an exploratory analysis against all strains regardless of match — a statistical recovery from a primary endpoint that could not be evaluated as designed.

Fluad Quadrivalent goes further. Its label carries this text in the highlights section: “This indication is approved under accelerated approval based on the immune response elicited by FLUAD QUADRIVALENT. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.” Fluad Quadrivalent was approved in 2020. The 2022-2023 label — the one in this installment — does not

describe results from a completed confirmatory trial. The product has been on the market for over five years on the basis of producing antibodies, without the confirmatory demonstration of clinical benefit that was the condition of approval.

> ASK YOUR DOCTOR
> *Is the flu vaccine I'm being offered approved based on prevention of influenza illness, or on production of antibodies? If the latter, what evidence exists that the antibody level correlates with clinical protection?*

The Annual Reformulation Problem

The mechanism of action section in every label contains a version of the same sentence. Flublok: “Antibodies against one influenza virus type or subtype confer limited or no protection against another. Furthermore, antibodies to one antigenic variant of influenza virus might not protect against a new antigenic variant of the same type or subtype. Frequent (usually annual) development of antigenic variants through antigenic drift is the virologic basis for seasonal epidemics and the reason for the usual replacement of one or more influenza virus strains in each year's influenza vaccine.” Fluarix, Flulaval, Flucelvax, Fluzone and Fluad repeat this language almost verbatim.

The product sold as Fluzone Quadrivalent in the 2025-2026 season contains different strains than the product sold as Fluzone Quadrivalent in the 2024-2025 season, which contained different strains than the 2023-2024 formula. Each year's formula is a strain selection made by the WHO and FDA months before the season begins, based on what the agencies describe as surveillance of circulating variants. The label's own mechanism section concedes that antibodies to a particular strain may not protect against a drifted version of the same strain.

No flu vaccine currently on the US market is tested for efficacy against the strains it actually contains in the year it is sold. The efficacy trials — where they exist at all — were conducted in prior seasons, against prior strains, and the manufacturer extrapolates. This is not a polemical characterisation. It is the structure the labels describe. The Flublok Study 3 trial was the 2007-2008 season. The Fluzone High-Dose Study 2 trial ran across the 2011-2012 and 2012-2013 seasons. The efficacy data carried in every current label refers to a product that is no longer being sold.

Fluarix Quadrivalent's efficacy trial (Trial 7, NCT01439360, conducted in 13 countries across Asia, Europe and Central America during the 2011-2012, 2012-2013, and subtropical 2012-2014 seasons in healthy children aged 6 through 35 months) reported overall vaccine efficacy of 49.8% against RT-PCR-confirmed influenza A or B, regardless of match (95% CI 41.8, 56.8). The Fluarix label elsewhere, discussing the trivalent formulation in an age

subgroup analysis, carries the admission that "the trial lacked statistical power to evaluate efficacy within age subgroups, the clinical significance of these results is unknown". Flulaval Quadrivalent's label carries an analogous statement at the end of its Trial 1 efficacy discussion: "Since only 67% of cases could be typed, the clinical significance of this result is unknown".

> ASK YOUR DOCTOR
> *What clinical trial evidence supports the efficacy of the specific flu vaccine formula I am being offered this season? If that trial was conducted in a different year with different strains, what is the basis for expecting the result to apply to this year's product?*

Adverse Reactions in the Clinical Trials

The labels report solicited local and systemic reactions collected during clinical trials, usually within 7 to 10 days of vaccination. In adults, roughly one in ten to one in four recipients reports systemic symptoms — headache, fatigue, muscle aches — in the days following vaccination. Injection site reactions affect between a third and half of adult recipients in most products, with rates running higher in children.

Figures from the labels' own adverse-reactions summaries: Fluzone Quadrivalent in adults 18 years and older — injection site pain 47%, myalgia 24%, headache 16%, malaise 11%. Fluzone Quadrivalent in adults 65+ — pain 33%, myalgia 18%, headache 13%, malaise 11%. Fluzone High-Dose Quadrivalent in adults 65+ — pain 41.3%, myalgia 22.7%, headache 14.4%, malaise 13.2%. Fluarix Quadrivalent in adults — pain 36%, muscle aches 16%, headache 16%, fatigue 16%. Flucelvax Quadrivalent in adults 18-64 — pain 28%, headache 16%, fatigue 12%, myalgia 11%, malaise 10%. Flucelvax in adults 65+ — erythema 10%, fatigue 11%, headache 10%, malaise 10%. Fluad Quadrivalent in adults 65+ — pain 16.3%, headache 10.8%, fatigue 10.5%. Flublok Quadrivalent in adults 18-49 — tenderness 48%, pain 37%, headache 20%, fatigue 17%, myalgia 13%, arthralgia 10%.

In children, rates generally run higher and include age-specific reactions. Fluzone Quadrivalent in children 3-8 years — pain 67%, erythema 34%, swelling 25%, myalgia 39%, malaise 32%, headache 23%. Fluzone in children 6-35 months — pain/tenderness 47-57%, irritability 47-54%, abnormal crying 33-41%, malaise 38%, drowsiness 31-38%, appetite loss 27-32%, fever 11-14%. Flulaval Quadrivalent in children 3-17 — pain 65% as the most common local reaction; in ages 5-17, muscle aches 29%, fatigue 22%, headache 22%, arthralgia 13%. Flulaval in children 6-35 months — pain 40%, irritability 49%, drowsiness 37%, loss of appetite 29%. Fluarix Quadrivalent in children 3-17 — pain 44%, redness 23%, swelling 19%; ages 6-17 systemic reactions were fatigue 20%, muscle aches 18%, headache 16%, arthralgia 10%. Fluarix in children 6-35 months — pain 17%, redness 13%, irritability 16%, loss of appetite 14%, drowsiness 13%. Flucelvax Quadrivalent in children 9-17 — pain 34%, erythema

14%, myalgia 15%, headache 14%. Flucelvax in children 6 months through 3 years — tenderness 28%, erythema 26%, induration 17%, ecchymosis 11%, irritability 28%, sleepiness 27%, diarrhoea 18%.

FluMist delivers intranasally and the reactogenicity profile reflects that. The most common solicited reactions at ≥10% and at least 5% greater than placebo were runny nose or nasal congestion across all approved ages, fever over 100°F in children 2-6, and sore throat in adults 18-49. In pooled paediatric studies, runny nose or nasal congestion ran 51-58%, decreased appetite 21%, irritability 21%, decreased activity 14%, sore throat 11%, fever over 100°F 13-16%.

These are the rates in closely monitored trial populations. Real-world reporting to healthcare providers is almost certainly lower, because most recipients do not attribute a headache or a day of fatigue to a vaccine received the prior morning.

A separate finding from the Afluria label adds another dimension. When Afluria is administered by the PharmaJet Stratis needle-free jet injector rather than needle and syringe — same vaccine, same dose, same antigen — the rates of local reactions roughly triple. Injection site tenderness runs 89.4% vs 77.9%, swelling 64.8% vs 19.7%, pain 64.4% vs 49.3%, redness 60.1% vs 19.2%, itching 28.0% vs 9.5%, and bruising 17.6% vs 5.3%. The systemic reaction rates are similar by either delivery method, and the immunogenicity endpoints are non-inferior — meaning the jet injector produces the same antibody response as the needle — but does so at the cost of substantially more injection-site reaction. The jet injector is not approved for use in children or in adults 65 and older due to lack of adequate data in those populations.

> ASK YOUR DOCTOR
> *If I develop a headache, fatigue or muscle aches in the three days following vaccination, would that be recorded in my medical record? Would it be reported to* VAERS?

What's in the Vial

The Afluria label carries a complete disclosure of what a single dose contains beyond the antigen. Per 0.5 mL dose of the current 2025-2026 formulation: sodium chloride, monobasic and dibasic sodium phosphate, potassium salts and calcium chloride as the buffer system. Residuals from the manufacturing process “may also contain”: sodium taurodeoxycholate up to 10 parts per million, ovalbumin (egg protein) under 1 microgram, sucrose under 10 micrograms, neomycin sulfate up to 61.5 nanograms, polymyxin B up to 10.5 nanograms, beta-propiolactone under 2.3 nanograms, and hydrocortisone up to 0.56 nanograms.

Beta-propiolactone is the chemical used to inactivate the virus particles. Sodium taurodeoxycholate is used to disrupt the inactivated viruses into “split virions”. Neomycin and polymyxin B are antibiotics added during manufacturing. Hydrocortisone is a corticosteroid. Ovalbumin is the residual egg protein from the embryonated chicken egg substrate. These are amounts the label discloses as potentially present after purification.

The other egg-based labels (Fluarix, Flulaval, Fluzone, Fluzone High-Dose) carry comparable residuals disclosures. Flucelvax, being cell culture-based, discloses MDCK cell protein, MDCK cell DNA, and beta-propiolactone. Flublok, being recombinant and grown in insect cells, discloses baculovirus and Spodoptera frugiperda cell proteins up to 19 micrograms, baculovirus and cellular DNA up to 10 nanograms, and Triton X-100 detergent up to 100 micrograms per dose. Fluad adds the MF59 adjuvant: squalene, polysorbate 80, and sorbitan trioleate. FluMist contains viable attenuated virus rather than inactivated antigen.

The thimerosal question sits separately. The single-dose presentations for 2025-2026 are free of thimerosal, consistent with ACIP's preference this season. The Afluria multi-dose vial, however, contains thimerosal as a preservative — “each 0.5 mL dose contains 24.5 mcg of mercury and each 0.25 mL dose contains 12.25 mcg of mercury”. The 0.25 mL paediatric dose is the one administered to infants 6 months through 35 months of age. ACIP's 2025-2026 recommendations state that children aged 18 and under, pregnant women, and all adults should receive only single-dose formulations free of thimerosal — but the multi-dose formulation remains FDA-approved and available, and the jet injector delivery for adults 18-64 requires use of the multi-dose vial. The label discloses the mercury content. It does not provide a comparison to any reference exposure level, nor any discussion of the evidence base for the preservative's safety in the doses administered.

> ASK YOUR DOCTOR
> *Which presentation of the flu vaccine am I receiving — single-dose or multi-dose? If multi-dose, does this contain thimerosal, and what is the mercury dose per injection? What other residual substances are present in the vial beyond the antigen?*

Post-Marketing Reactions: What Was Discovered After Approval

The post-marketing sections of these labels describe events reported during real-world use, after approval. The manufacturers preface these lists with the caveat that causation cannot be reliably established from spontaneous reports, but the events are included because of “temporal relationship, biologic plausibility of a causal relationship”, and seriousness. What appears on these lists, then, is what the manufacturers judged substantial enough to include.

The post-marketing list for Fluarix and Flulaval together includes: Guillain-Barré syndrome, convulsion, encephalomyelitis, facial palsy, myelitis, neuritis, neuropathy, hypoesthesia, syncope, anaphylactic reaction including shock, hypersensitivity, serum sickness, lymphadenopathy, tachycardia, vertigo, conjunctivitis and various eye reactions, swelling of the mouth, throat and tongue, asthma, bronchospasm, dyspnea, respiratory distress, stridor, encephalopathy, limb paralysis, muscle weakness, arthritis, and Stevens-Johnson syndrome-class reactions.

Fluzone Quadrivalent adds thrombocytopenia, optic neuritis or neuropathy, brachial neuritis, transverse myelitis, Bell's palsy, vasculitis, ocular hyperaemia, wheezing, Stevens-Johnson syndrome, and febrile convulsions as a separate entry alongside the new Section 5.4 warning.

Flucelvax adds presyncope, paraesthesia and extensive swelling of the injected limb.

Fluad Quadrivalent's post-marketing list runs long. Blood and lymphatic: thrombocytopenia with some cases showing platelet counts below 5,000 per cubic millimetre — a level at which spontaneous bleeding is a concern and platelet transfusion would normally be considered. Nervous system: encephalomyelitis, Guillain-Barré syndrome, convulsions, neuritis, neuralgia. Skin: erythema multiforme, generalised skin reactions. Vascular: vasculitis, renal vasculitis. Administration site: extensive swelling lasting more than one week, and cellulitis-like reactions extending more than 10 cm and lasting more than one week.

FluMist's post-marketing list includes pericarditis, hypersensitivity reactions including anaphylactic reaction and facial oedema, and an entry that appears on no other label in this set — “Exacerbation of symptoms of mitochondrial encephalomyopathy (Leigh syndrome)”.

The Afluria post-marketing section adds several findings. Nervous system disorders: neuralgia, paraesthesia, convulsions (including febrile seizures), dizziness, encephalomyelitis, encephalopathy, neuritis or neuropathy, transverse myelitis, Guillain-Barré syndrome, syncope and presyncope. Blood and lymphatic: thrombocytopenia. Immune system: serum sickness alongside anaphylactic shock. Vascular disorders: “Vasculitis which may be associated with renal involvement”. The kidney involvement is specific — vasculitis of the small vessels of the kidney can cause acute kidney injury.

None of these events appeared in the clinical trials at detectable rates. They emerged once the vaccines were administered to populations much larger than the trial cohorts, often with underlying conditions the trials had excluded.

ASK YOUR DOCTOR

Which of the post-marketing adverse events on this product's label have you seen in your practice? How would I distinguish a serum sickness reaction or Guillain-Barré onset from other symptoms in the weeks after vaccination?

FluMist as Special Case

FluMist is classified as a live attenuated vaccine — the label states that the strains contained in the nasal spray are weakened but viable influenza viruses, not inactivated fragments. The label acknowledges this in Section 12.2 (Pharmacodynamics) and in the warnings.

Two clinical trials in young children produced findings severe enough to appear in the highlights section. In Study MI-CP111, children 6 through 23 months of age who received FluMist were hospitalised at 4.2% (84/1,992) versus 3.2% (63/1,975) for the inactivated injectable comparator. Wheezing requiring bronchodilator therapy or accompanied by respiratory distress or hypoxia occurred in 5.9% (117/1,992) of FluMist recipients in this age group versus 3.8% (75/1,975) for the comparator. In post-hoc analysis, children 6-11 months had hospitalisation rates of 6.1% for FluMist versus 2.6% for the comparator. These findings are why FluMist is not approved for children under 2. The label: “In clinical trials, risks of hospitalization and wheezing were increased in children younger than 2 years of age who received FluMist.”

In a separate HMO-based study (AV019), children younger than 5 years of age who received FluMist had a relative risk of 3.53 for asthma events (90% CI: 1.1, 15.7) compared to placebo. This finding is in the clinical trials section, not a footnote.

The shedding data is in Section 12.2. A transmission study in a daycare setting with children 8 through 36 months of age found that at least one vaccine strain was isolated from 80% of FluMist recipients, with strains recovered from 1 to 21 days post-vaccination and a mean duration of shedding of 7.6 days (± 3.4 days). In the same study, one placebo subject developed mild symptomatic Type B virus infection that was confirmed by genetic sequencing as a transmitted vaccine strain from a FluMist recipient in the same playgroup. The label estimates the probability of a young child acquiring vaccine virus from close contact with a single FluMist vaccinee in a daycare setting at 0.58% per close contact, or 2.4% including unconfirmed possible transmissions.

The label draws out its own clinical implication: recipients should be counselled that what it calls vaccine virus is recoverable from nasal secretions for more than a week after vaccination, and that transmission of what it calls vaccine strain to close contacts — particularly immunocompromised individuals, for whom the label says live virus exposure would be dangerous — is a documented possibility. The label advises avoiding close contact

with severely immunocompromised persons for at least 2 weeks following FluMist administration.

> ASK YOUR DOCTOR
> *If I or someone in my household receives FluMist, what household members might be at risk from shedding? How long should we avoid close contact with immunocompromised relatives or newborns?*

What the Labels Admit Has Not Been Studied

Across all nine labels, Section 13 (Nonclinical Toxicology) contains a version of the same sentence. Fluzone Quadrivalent: “Fluzone Quadrivalent has not been evaluated for carcinogenic or mutagenic potential, or for impairment of male fertility.” Flucelvax: “FLUCELVAX has not been evaluated for carcinogenic or mutagenic potential, or for impairment of male fertility.” Fluarix: “FLUARIX QUADRIVALENT has not been evaluated for carcinogenic or mutagenic potential or male infertility in animals.” Flulaval: “FLULAVAL QUADRIVALENT has not been evaluated for carcinogenic, mutagenic potential, or male infertility.” Fluzone High-Dose Quadrivalent: “has not been evaluated for carcinogenic or mutagenic potential.” Fluad Quadrivalent: “has not been evaluated for carcinogenic or mutagenic potential.” Flublok Quadrivalent: “has not been evaluated for carcinogenic or mutagenic potential, or for impairment of male fertility in animals.” Afluria: “AFLURIA has not been evaluated for carcinogenic or mutagenic potential, or male infertility in animals.” FluMist: “FluMist has not been evaluated for its carcinogenic or mutagenic potential.”

Nine products. Zero evaluations for cancer-causing potential. Zero evaluations for mutagenic potential. Zero evaluations for impairment of male fertility.

The pregnancy sections contain parallel admissions. Fluzone Quadrivalent: “Available data with Fluzone Quadrivalent use in pregnant women are insufficient to inform vaccine-associated risks in pregnancy.” Flublok: “Available data on Flublok Quadrivalent and Flublok (trivalent formulation) administered to pregnant women are insufficient to inform vaccine-associated risks in pregnant women. There were no developmental studies of Flublok Quadrivalent formulation performed in animals.” Fluarix and Flulaval rely on registry data that was still being collected at the time of label revision. Pregnancy registries exist for several products but the labels do not present completed analyses with risk estimates.

The lactation sections are uniform. For each of the injectable products: “It is not known whether [the vaccine] is excreted in human milk. Data are not available to assess the effects of [the vaccine] on the breastfed infant or on milk production/excretion.”

Paediatric use is limited across products. Flublok: not studied in children under 18, with a stronger statement that a trial in 6-month to 3-year-olds showed “diminished

hemagglutinin inhibition responses" suggesting "Flublok would not be effective in children younger than 3 years of age". Fluad: not studied in anyone under 65. FluMist: not approved for children under 2 due to wheezing and hospitalisation findings.

Drug interactions sections are similarly thin. Flublok: "Data evaluating the concomitant administration of Flublok Quadrivalent with other vaccines are not available." Flulaval: "There are insufficient data to assess the concomitant administration of FLULAVAL QUADRIVALENT with other vaccines." Similar language appears in other labels. In clinical practice, flu vaccines are routinely co-administered with COVID-19 vaccines, pneumococcal vaccines, shingles vaccines, and other injections during a single visit. The labels do not carry efficacy or safety data for these combinations.

Immunocompromised persons: the labels uniformly state that the immune response may be diminished, and FluMist specifically warns that "effectiveness of FluMist has not been studied in immunocompromised persons". Geriatric populations are studied for most products, but the Flublok label concedes that data from the elderly subset in Study 2 "are insufficient to determine whether elderly subjects respond differently from younger subjects".

Long-term outcomes — effects beyond the period of active trial follow-up, which is typically 6 months — are not evaluated in any of the labels. There is no information on cumulative effects from annual repeat vaccination over years or decades. There is no information on interactions between flu vaccination and later diagnosis of chronic conditions.

> ASK YOUR DOCTOR
> *Given that these vaccines have not been evaluated for carcinogenic, mutagenic or fertility effects, and the long-term effects of repeated annual vaccination are not in the label, what evidence supports the safety of receiving these shots every year for decades?*

Unique Warnings and Outlier Findings

A few findings are specific to single products rather than shared across the class.

Fluad Quadrivalent's post-marketing section notes thrombocytopenia, some cases severe with platelet counts less than 5,000 per mm^3. This is a distinct finding for the adjuvanted product — platelet counts at this level carry substantial bleeding risk. The adjuvant in Fluad is MF59, an oil-in-water emulsion containing squalene, polysorbate 80 and sorbitan trioleate.

FluMist's post-marketing list includes exacerbation of symptoms of mitochondrial encephalomyopathy (Leigh syndrome) — a category of rare genetic mitochondrial disorders. The label does not explain the mechanism but notes the association strongly enough to

include it.

Flublok's trivalent trial experience included one case of pleuropericarditis assessed as "possibly related" to the vaccine (Study 3 SAE analysis). The quadrivalent Flublok trial reported no cases judged related.

Fluzone Quadrivalent's post-marketing list includes Stevens-Johnson syndrome, a severe mucocutaneous reaction with potential for fatal outcome. This does not appear on all labels.

FluMist's label specifically excludes use in persons receiving aspirin or salicylate therapy, due to concerns about Reye's syndrome in children and adolescents.

> ASK YOUR DOCTOR
> *Does the specific flu vaccine I am being offered carry any warnings that are unique to this product rather than common to the class?*

Drug Interactions

Every label in this set is thin on drug interaction data. The broad structure is: immunosuppressive therapies may diminish immune response to the vaccine; concomitant administration with other vaccines is either limited in data or not studied at all. The Flublok label states simply: "Data evaluating the concomitant administration of Flublok Quadrivalent with other vaccines are not available."

For the most common real-world combination — flu vaccine plus COVID-19 vaccine at the same visit — the labels carry no specific safety or efficacy data. The CDC recommends co-administration based on general vaccine co-administration principles, but the FDA-approved label does not characterise this combination.

For patients taking immunomodulatory drugs — anti-TNF therapies, JAK inhibitors, methotrexate, rituximab, chemotherapy — the labels uniformly warn of diminished response but do not specify dosing adjustments, timing recommendations or alternative vaccination strategies.

> ASK YOUR DOCTOR
> *If I am being offered the flu vaccine at the same visit as another vaccine, is there label data supporting the safety and efficacy of that combination, or is the co-administration based on general principles?*

What the Labels, Read Together, Are Saying

Step back from the specific percentages and the individual product findings and this is what the nine labels, taken together, describe.

The vaccines are approved to prevent illness caused by the particular strains the manufacturer selected for that season's formula. They are not approved to prevent flu symptoms in general, to reduce hospitalisation, to reduce mortality, or to reduce transmission to others. Every label acknowledges this specific indication, and every label carries the reminder that "vaccination may not protect all recipients".

Three of the nine products — Fluzone High-Dose, Flublok and Fluad — were approved on the basis that they produce antibody levels comparable to older products, not on the basis of new trials showing they prevent influenza illness. The Afluria label, in its own mechanism-of-action section, states that antibody titres after flu vaccination "have not been correlated with protection from influenza virus" and have only been associated with protection in about half of subjects in some studies. The surrogate on which three of the products are approved is, by another product's label's own description, not a reliable predictor of the outcome the vaccines are sold to achieve.

The efficacy data in every current label comes from older seasons — 2007-2008, 2011-2012, 2011-2014 — against strains that are no longer circulating. No flu vaccine on the US market this winter has been trial-tested against the strains it actually contains. Each year's formula is a strain selection made months before the season begins, and the labels' own mechanism sections concede that antibodies against one strain may not protect against a drifted variant of the same strain. The structure of the program is: the product is reformulated every year, the reformulation is not tested, and the reformulation is administered to tens of millions of people.

One month before this installment, a new warning was added to three of the most-administered labels: an observational study found children aged 6 months through 4 years had a 97% to 194% increase in relative risk of febrile seizures in the first day after vaccination. The warning is in the label. The product remains on the recommended schedule for that age group, with no other change. Parents administering the shot to their child this winter are not being shown the warning at the point of administration.

None of the nine products have been evaluated for cancer-causing potential, for genetic damage, or for impairment of fertility. Long-term effects of receiving these injections every year for decades are not characterised in any of the labels. The pregnancy data is either insufficient (most products) or drawn from registries smaller than the populations in which the vaccine is administered. Lactation data, for every injectable product, states simply that it is not known whether the vaccine is excreted in human milk.

This is the picture you are walking into when you walk into a doctor's office and are offered a flu shot. None of these findings is hidden; all of them are in the FDA-approved prescribing information for the product being administered. Most patients never see the prescribing information. The questions in the next section are designed to bring the contents of that document into the conversation.

Questions to Take to Your Doctor

The questions integrated throughout this installment, consolidated here for reference:

1. Was I informed of the March 2026 febrile seizure warning before my child received a flu vaccine? If not, why not? How will I be able to distinguish a post-vaccine febrile seizure from any other seizure, and what should I do if it occurs?
2. Is the flu vaccine I'm being offered approved based on prevention of influenza illness, or on production of antibodies? If the latter, what evidence exists that the antibody level correlates with clinical protection?
3. What clinical trial evidence supports the efficacy of the specific flu vaccine formula I am being offered this season? If that trial was conducted in a different year with different strains, what is the basis for expecting the result to apply to this year's product?
4. If I develop a headache, fatigue or muscle aches in the three days following vaccination, would that be recorded in my medical record? Would it be reported to VAERS?
5. Which of the post-marketing adverse events on this product's label have you seen in your practice? How would I distinguish a serum sickness reaction or Guillain-Barré onset from other symptoms in the weeks after vaccination?
6. If I or someone in my household receives FluMist, what household members might be at risk from shedding? How long should we avoid close contact with immunocompromised relatives or newborns?
7. Given that these vaccines have not been evaluated for carcinogenic, mutagenic or fertility effects, and the long-term effects of repeated annual vaccination are not in the label, what evidence supports the safety of receiving these shots every year for decades?
8. Does the specific flu vaccine I am being offered carry any warnings that are unique to this product rather than common to the class?
9. If I am being offered the flu vaccine at the same visit as another vaccine, is there label data supporting the safety and efficacy of that combination, or is the co-administration based on general principles?

10. Which presentation of the flu vaccine am I receiving — single-dose or multi-dose? If multi-dose, does this contain thimerosal, and what is the mercury dose per injection? What other residual substances are present in the vial beyond the antigen?
11. Can I see the package insert for the specific product being administered today, before the shot?
12. Will you document any symptoms I experience in the two weeks after this vaccination as potentially vaccine-related?
13. If Fluad Quadrivalent was approved on condition of a confirmatory trial, is that trial now complete? What were the results?

> **Disclaimer**
> This series is not medical advice. It is a reading of FDA-approved prescribing information for the vaccines under discussion, intended to help patients read what is written and ask better questions of their healthcare providers. All factual statements are drawn directly from the labels cited.

Sources

All prescribing information is available at www.fda.gov/drugsatfda.

- Afluria (Influenza Vaccine), Seqirus Pty Ltd / Seqirus USA Inc., 2025-2026 Formula (Trivalent). Initial U.S. Approval: 2007. BLA STN 125254.
- Fluzone Quadrivalent (Influenza Vaccine), Sanofi Pasteur Inc., 2025-2026 Formula. Initial U.S. Approval: 2013. BLA STN 125127.
- Fluzone High-Dose Quadrivalent (Influenza Vaccine), Sanofi Pasteur Inc. BLA STN 125127.
- Fluarix Quadrivalent (Influenza Vaccine), GlaxoSmithKline Biologicals, 2019-2020 Formula. Initial U.S. Approval: 2012. BLA STN 125127.
- Flulaval Quadrivalent (Influenza Vaccine), ID Biomedical Corporation of Quebec (GSK), 2020-2021 Formula. Initial U.S. Approval: 2013. BLA STN 125163.
- Flucelvax Quadrivalent (Influenza Vaccine), Seqirus Inc., 2025-2026 Formula. Initial U.S. Approval: 2012. BLA STN 125408.
- Fluad Quadrivalent (Influenza Vaccine, Adjuvanted), Seqirus Inc., 2022-2023 Formula. Initial U.S. Approval: 2020. BLA STN 125510.
- Flublok Quadrivalent (Influenza Vaccine), Protein Sciences Corporation / Sanofi Pasteur Inc., 2020-2021 Formula. Initial U.S. Approval: 2013. BLA STN 125285/419.
- FluMist Quadrivalent (Influenza Vaccine Live, Intranasal), MedImmune LLC (AstraZeneca), 2025-2026 Formula. Initial U.S. Approval: 2003. BLA STN 125020.

Note on scope: Beginning with the 2024-2025 season, the FDA transitioned all US flu vaccines from quadrivalent to trivalent, dropping the B/Yamagata lineage. The current 2025-2026 products are trivalent reformulations of the vaccines whose quadrivalent labels are cited above where quadrivalent labels were analysed. Afluria is cited from its current 2025-2026 trivalent label. Flublok's age indication was expanded in March 2025 from 18+ to 9+. FluMist was approved for self- or caregiver administration in September 2024.