

Flublok[®]
Influenza Vaccine

FORMULARY KIT

sanofi



INDICATION AND IMPORTANT SAFETY INFORMATION FOR FLUBLOK[®] (INFLUENZA VACCINE)

FLUBLOK[®] (INFLUENZA VACCINE)

Flublok is a vaccine indicated for active immunization for the prevention of disease caused by influenza A virus subtypes and influenza type B virus represented by antigens contained in the vaccine. Flublok is approved for use in individuals 9 years of age and older.

IMPORTANT SAFETY INFORMATION FOR FLUBLOK[®] (INFLUENZA VACCINE)

Do not administer Flublok to anyone with a history of severe allergic reactions (e.g., anaphylaxis) to any component of the vaccine.

Appropriate medical treatment must be immediately available to manage potential anaphylactic reactions following administration of Flublok.

If Guillain-Barré syndrome has occurred within 6 weeks of receipt of a prior influenza vaccine, the decision to give Flublok should be based on careful consideration of the potential benefits and risks.

If Flublok is administered to immunocompromised persons, including those receiving immunosuppressive therapy, the immune response may be diminished.

Vaccination with Flublok may not protect all recipients.

Syncope (fainting) has been reported following vaccination with Flublok. Procedures should be in place to avoid injury from fainting.

In children 9 through 17 years of age who received Flublok Quadrivalent, the most common solicited injection-site adverse reaction was pain; the most common solicited systemic adverse reactions were myalgia, headache, and malaise. In adults 18 through 64 years of age who received Flublok, the most common injection site adverse reaction was pain; the most common solicited systemic adverse reactions were headache, fatigue, and myalgia. In adults 65 years of age and older who received Flublok, the most common injection-site adverse reaction was pain; the most common solicited systemic adverse reactions were fatigue and headache. Other adverse reactions may occur.



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FLUBLOK[®] PRODUCT MONOGRAPH

EXECUTIVE SUMMARY

Influenza is a contagious respiratory illness that can range from mild to severe.¹ Different strains of the virus circulate every year.² Some groups of people are at higher risk for other complications from influenza that can result in hospitalization³:

- Adults aged ≥50 years
- Residents of nursing homes and other long-term care facilities
- People who are immunocompromised or have certain chronic conditions
- People who are or will be pregnant during influenza season

Routine annual vaccination is recommended to prevent illness from influenza and to reduce the severity of illness and risk for hospitalization for those who become infected.^{4,5} In the 2023-2024 influenza season, 44.9% of adults received at least 1 dose of influenza vaccine. Vaccination coverage was lower for all age groups compared with the 2022-2023 influenza season. White adults had higher vaccination coverage than non-Hispanic Black, Hispanic, and non-Hispanic adults of other or multiple races.⁶

There is a need for broad protection against different strains of influenza virus in all adult patients, especially in older adults and in individuals with certain chronic health conditions who are at higher risk for complications.

Flublok[®] is a single-dose vaccine containing recombinant hemagglutinin proteins from the 3 strains of influenza virus specified by health authorities for inclusion in the annual seasonal vaccine.⁷ Recombinant DNA technology ensures identical antigenic match with WHO- and FDA-selected influenza strains and avoids potential mutations in production that can reduce the protection of flu vaccines created with other technologies.⁸

The vaccine efficacy of Flublok (trivalent) was demonstrated vs placebo in a clinical study, and the relative vaccine efficacy of Flublok (quadrivalent) was demonstrated vs a US-licensed comparator in a separate clinical study. The safety of Flublok (trivalent) was analyzed in 4 randomized, placebo- or active-controlled clinical trials, and the safety of Flublok (quadrivalent) was also established vs a US-licensed comparator.⁷ The real-world efficacy of Flublok (quadrivalent) has been evaluated in a large retrospective study of the Medicare claims system⁹ and 2 studies of 2 large health systems in the United States: the Kaiser Permanente Northern California (KPNC) health system and the University of Pittsburgh Medical Center (UPMC) health system.^{10,11}

Abbreviations: DNA, deoxyribonucleic acid; FDA, US Food and Drug Administration; WHO, World Health Organization.



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OVERVIEW OF INFLUENZA

WHAT IS INFLUENZA?

Influenza is a contagious respiratory illness that infects the nose and throat, and sometimes the lungs, and can range from mild to severe. The transmission of influenza occurs when a susceptible individual comes into contact with droplets that enter the air when an infected individual coughs, sneezes, or talks. These droplets can land in the mouths or noses, or possibly be inhaled into the lungs, of people who are in close proximity to an infected individual. A person may also get influenza by touching their own mouth, nose, or possibly their eyes after touching a surface or object that has influenza virus on it.¹

THERE ARE **4** TYPES OF
INFLUENZA VIRUSES²:



Influenza A and B viruses cause seasonal epidemics of disease (known as flu season) almost every winter in the United States. Influenza A viruses are the only influenza viruses known to cause flu pandemics.²

Influenza A viruses are divided into subtypes based on 2 proteins on the surface of the virus: hemagglutinin (H or HA) and neuraminidase (N or NA). There are 18 different H subtypes (H1 through H18) and 11 different N subtypes (N1 through N11). There are many influenza A subtype combinations due to the propensity for virus reassortment, a process by which influenza viruses swap gene segments.²

INFLUENZA VIRUSES ARE CONSTANTLY CHANGING DUE TO 2 DIFFERENT MECHANISMS¹²

ANTIGENIC DRIFT:

- Small changes that occur continually over time in the genes of influenza viruses that ultimately alter the surface proteins (antigens) HA and NA, which are recognized by the immune system
- The accumulation of several small changes over time can result in antigenically different viruses

ANTIGENIC SHIFT:

- A less common and abrupt major change in the genes of influenza viruses that results in new HA and/or NA proteins, leading to in a new infectious subtype

Seasonal flu vaccines are formulated to protect against influenza viruses known to cause epidemics and are based on the current subtypes of influenza A and B that routinely circulate in the population. Starting in the 2024-2025 flu season, the FDA has recommended flu vaccines to be trivalent and include^{1,13}



- 1 influenza A(H1N1) virus
- 1 influenza A(H3N2) virus



- 1 influenza B/Victoria lineage virus

In previous years, quadrivalent vaccines were formulated to include a second influenza B subtype, B/Yamagata lineage, which the FDA and WHO have advised to remove starting in the 2024-2025 influenza season due to evidence that it no longer poses a threat to public health.^{2,13,14}



EPIDEMIOLOGY OF INFLUENZA

DURING THE 2023-2024 INFLUENZA SEASON IN THE UNITED STATES, IT IS ESTIMATED THAT INFLUENZA CONTRIBUTED TO SYMPTOMATIC ILLNESSES, MEDICAL VISITS, HOSPITALIZATIONS, AND DEATHS¹⁵

AGE	SYMPTOMATIC ILLNESSES	MEDICAL VISITS	HOSPITALIZATIONS	DEATHS
5 TO 17 YEARS	~9.3 million	~4.8 million	~25,500	~250
18 TO 49 YEARS	~16.3 million	~6.0 million	~92,000	~2,700
50 TO 64 YEARS	~9.0 million	~3.9 million	~95,900	~5,700
≥65 YEARS	~2.6 million	~1.5 million	~237,300	~19,000

In the United States, influenza-associated hospitalization rates are typically highest in the elderly compared with other age groups.¹⁵

Racial and ethnic disparities can be seen in outcomes, hospitalization rates, and mortality rates^{16,17}

- The age-adjusted mortality rate for influenza was higher in non-Hispanic Black adults than in non-Hispanic White adults^{17a}
- From the 2009-2010 through 2022-2023 influenza seasons (excluding 2020-2021), Black, Hispanic, and American Indian/Alaska Native people consistently had more serious outcomes and higher hospitalization rates than White people¹⁶
 - During most influenza seasons, age-adjusted hospitalization rates were highest among Black adults^{16,b}

AGE-ADJUSTED HOSPITALIZATION RATES FROM 2009-2023 WERE¹⁶

 **1.8X** HIGHER AMONG BLACK ADULTS

 **1.4X** HIGHER AMONG AMERICAN INDIAN/ALASKA NATIVE ADULTS

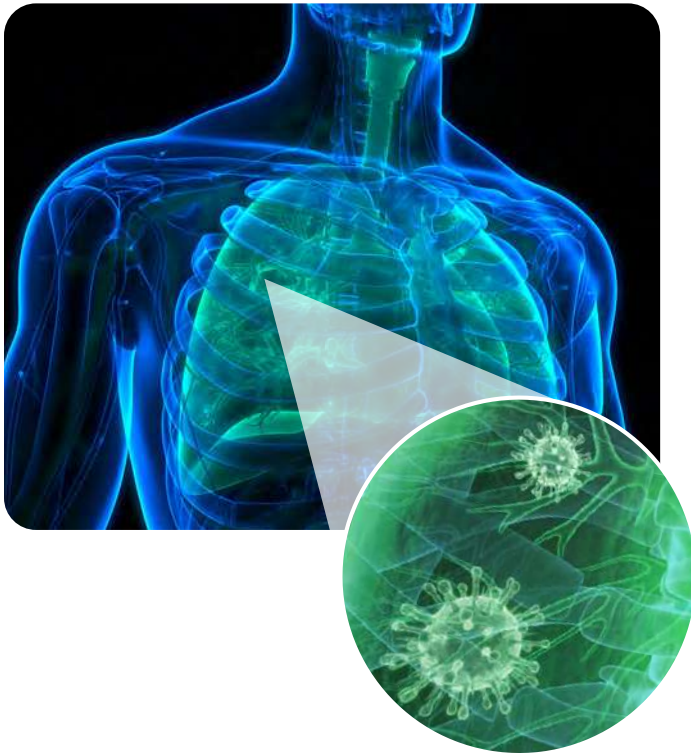
 **1.2X** HIGHER AMONG HISPANIC OR LATINO ADULTS

^aMortality rates were determined using the Centers for Disease Control and Prevention (CDC) database for Multiple Cause of Death between 1999 and 2018 for non-Hispanic Black and non-Hispanic White decedents aged ≥25 years with an *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*, code for influenza (J09-J11) and pneumonia (J12-J18).¹⁷

^bData from the Influenza-Associated Hospitalization Surveillance Network (FluSurv-NET), which conducts all-age, population-based surveillance for laboratory-confirmed influenza-associated hospitalizations in selected states, representing approximately 8%-9% of the US population.¹⁸



MECHANISM OF DISEASE IN INFLUENZA



Human influenza virus infection replicates primarily in the respiratory epithelium, but can also replicate in other cell types like immune cells.¹⁹ HA is a glycoprotein located on the surface of influenza viruses and is responsible for binding to host cell surfaces and mediating viral genome entry into the cell.²⁰

The primary mechanism of influenza pathophysiology is a result of lung inflammation that is further exacerbated by the body's immune response, which could lead to lung compromise, severe respiratory distress, and, ultimately, multiorgan failure.¹⁹

The influenza virus infects both the upper and lower respiratory tracts. One of the key criteria in determining the severity of influenza infection is the degree to which the lower respiratory tract has been affected. The body's overall response to the infection represents a physiological failure as the lungs could lose their ability to exchange gas.¹⁹



CLINICAL BURDEN OF INFLUENZA

<p>THE MOST COMMON SYMPTOMS OF INFLUENZA ARE²¹</p>	<ul style="list-style-type: none"> • Fever • Cough • Sore throat 	<ul style="list-style-type: none"> • Runny or stuffy nose • Muscle or body aches • Headaches 	<ul style="list-style-type: none"> • Fatigue • Vomiting • Diarrhea
<p>OTHER SYMPTOMS OF INFLUENZA CAN INCLUDE²²</p>	<ul style="list-style-type: none"> • Dyspnea • Sputum production 	<ul style="list-style-type: none"> • Chills • Myalgia 	<ul style="list-style-type: none"> • Chest pain • Croup

Moderate complications include²¹

- Sinus infections
- Ear infections

Serious complications include²¹

- Pneumonia
- Myocarditis
- Encephalitis
- Myositis
- Rhabdomyolysis
- Respiratory failure
- Kidney failure
- Sepsis

INFLUENZA INFECTION MAY INCREASE THE RISK OF STROKE, HEART ATTACK, AND PNEUMONIA

IN ADULTS



~8X INCREASED RISK OF STROKE^{23,a}



~10X INCREASED RISK OF HEART ATTACK^{23,a}

IN CHILDREN



8X INCREASED RISK OF PNEUMONIA^{23,b}

^aIn the first 1-3 days after infection.²³

^bWithin 1 week after influenza infection, based on a study of children aged 0 to 14 years.²⁴



CLINICAL BURDEN OF INFLUENZA (CONTINUED)

Some populations are at higher risk for hospitalization or even death because they can be more likely to develop complications from severe cases of influenza. These populations include³

- Adults aged ≥50 years
- People who are immunocompromised
- People who are or will be pregnant during the influenza season
- Residents of nursing homes and other long-term care facilities
- People with obesity (body mass index ≥40 kg/m²)
- Adults and children with chronic pulmonary, cardiovascular, renal, hepatic, neurologic, hematologic, or metabolic disorders

PEOPLE WITH DIABETES ARE

 **3X** MORE LIKELY TO BE HOSPITALIZED²⁵

 **4X** MORE LIKELY TO BE ADMITTED TO THE INTENSIVE CARE UNIT²⁵

 **2X** MORE LIKELY TO DIE AFTER BEING HOSPITALIZED WITH INFLUENZA²⁶



Adults with type 2 diabetes have a **74% increased risk** of abnormal glyceemic events after influenza infection.²⁷

The most frequently diagnosed influenza-related complications in patients hospitalized for severe influenza are^{28,a}



- Pneumonia
- Acute exacerbation of chronic obstructive pulmonary disease (COPD) or asthma
- Acute bronchitis



- Cardiovascular complications, such as congestive heart failure, acute coronary syndrome, and atrial fibrillation

3 DAYS

was the median duration of oxygen therapy for patients hospitalized with severe influenza^{27,a}

^aResults from a prospective, observational cohort study conducted among hospitalized adults with laboratory-confirmed influenza. Patients were aged ≥18 years and were admitted to 2 hospital medical departments between January 1, 2007, and December 31, 2008.²⁸



CLINICAL BURDEN OF INFLUENZA (CONTINUED)

In a group of patients who died from severe influenza, the median time from admission to death was 7 days.^{28,a}

The main conditions contributing to death were²⁸



- Pneumonia
- Respiratory failure related to underlying COPD or asthma



- Sepsis



- Acute cardiovascular events



• Of 754 patients hospitalized for influenza, **5.2% of patients died**^{28,a}

• Older age, male sex, presence of comorbid illnesses, being a nursing home resident, and need for ventilatory support were **factors associated with death in individuals hospitalized for severe influenza**²⁸

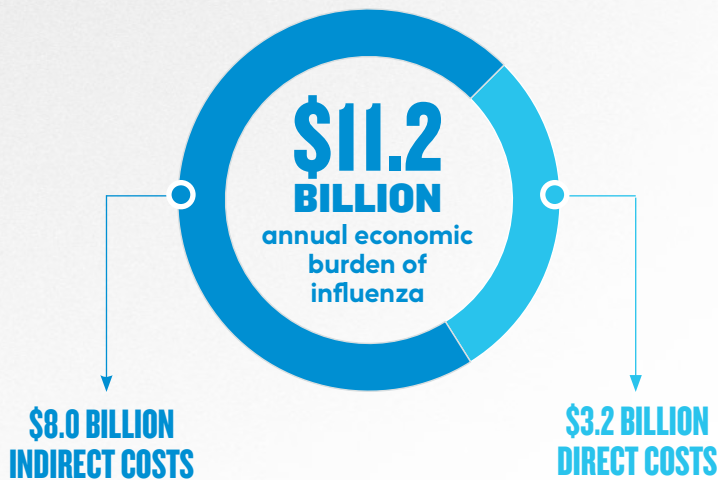
^aResults from a prospective, observational cohort study conducted among hospitalized adults with laboratory-confirmed influenza. Patients were aged ≥ 18 years and were admitted to 2 hospital medical departments between January 1, 2007, and December 31, 2008.²⁸



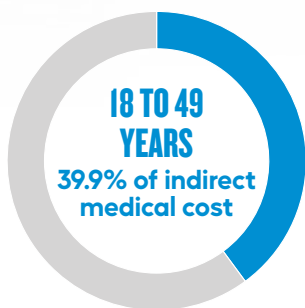
ECONOMIC BURDEN OF INFLUENZA

The CDC estimates that influenza has resulted in 9.3 million to 41 million illnesses, 120,000 to 710,000 hospitalizations, and 6,300-52,000 deaths annually between 2010 and 2024.²⁹

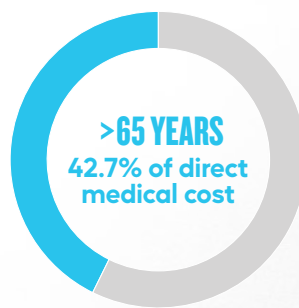
**IN 2015, THE TOTAL ANNUAL ECONOMIC BURDEN
OF INFLUENZA WAS \$11.2 BILLION^{30,a}**



The age group with the largest share of **INDIRECT COSTS**



The age group with the largest share of **DIRECT COSTS**



This was driven primarily by hospitalization costs (\$1.3 billion)

THE AGE GROUPS CONTRIBUTING MOST TO THE TOTAL COSTS



The population in the 18-to-49-years age group represents the largest share of the total population (43%)

- Aggregated cost data showed that overall direct costs attributable to influenza increased with age and were significantly higher in the elderly than in adults aged <65 years³⁰
- Individual hospitalization costs due to influenza in the general population increased with age among patients aged <65 years³¹

^aAll costs are reported in 2015 US dollars. The medical care component of the US Consumer Price Index was used to inflate costs from previous years to 2015 US dollars. Direct medical costs were calculated by multiplying the estimated age-specific average annual number of events by the unit cost for a given outcome (eg, influenza hospitalizations x cost of influenza hospitalization).³⁰



CURRENT MANAGEMENT STRATEGY

Most people who are infected with influenza have mild illness that does not require medical care or antiviral medications. Staying home, resting, and avoiding contact with others is recommended. For those who are at higher risk of complications or have more severe symptoms, antiviral medications may be prescribed. Further respiratory complications can result in hospitalization and other respiratory management.³²

Vaccination can prevent illness from influenza and reduce the severity of illness and risk of hospitalization for those who become infected.⁵ Routine annual influenza vaccination is recommended for people aged ≥6 months who do not have contraindications. As of 2023, the Advisory Committee on Immunization Practices (ACIP) recommends that adults aged ≥65 years receive any of the higher-dose or adjuvanted influenza vaccines, including⁴

- High-dose inactivated influenza vaccine (HD-IIV4)
- Recombinant influenza vaccine (RIV4)
- Adjuvanted inactivated influenza vaccine (aIIV4)

If none of these 3 vaccines is available at a vaccination opportunity, then any other age-appropriate influenza vaccine should be used.⁴

As of March 5, 2024, the FDA's Vaccines and Related Biological Products Advisory Committee recommended that all flu vaccines in the United States starting in the 2024-2025 flu season be trivalent vaccines and include an A(H1N1), an A(H3N2), and a B/Victoria-lineage vaccine virus. B/Yamagata viruses, which are included in current quadrivalent flu vaccines, are no longer actively circulating, so their inclusion in flu vaccines is no longer recommended.¹³

UNMET NEED

IN THE 2023-2024 FLU SEASON

44.9% OF ADULTS RECEIVED A
FLU VACCINE⁶

Influenza vaccination has been consistently higher among White and Asian adults compared with Black and Hispanic adults since the 2010-2011 season.¹⁶

- In the 2023-2024 flu season, White adults had higher flu vaccination coverage than non-Hispanic Black, Hispanic, and non-Hispanic adults of other or multiple races⁶

VACCINATION COVERAGE COMPARED WITH THE 2022-2023 SEASON⁶

 **2.4%** LOWER AMONG ADULTS AGED 18 TO 49 YEARS

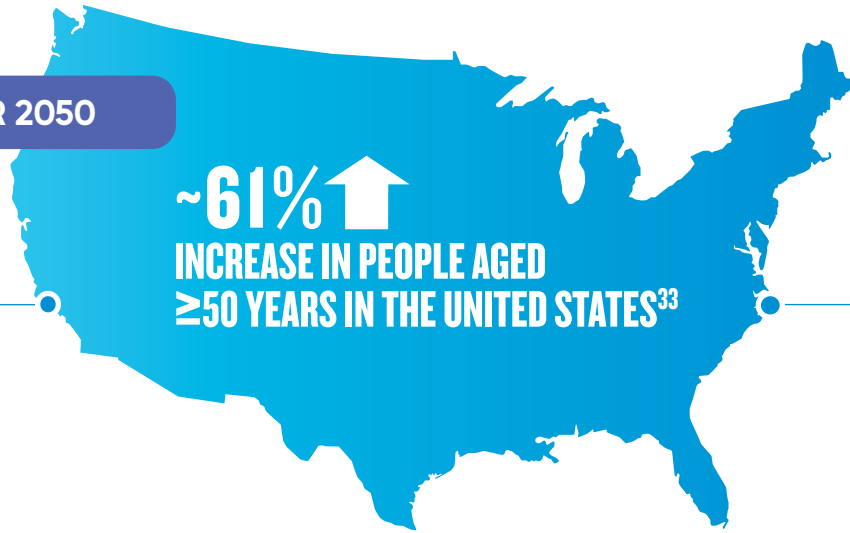
 **3.9%** LOWER AMONG ADULTS AGED 50 TO 64 YEARS

 **Flat** AMONG ADULTS AGED ≥65 YEARS



UNMET NEED (CONTINUED)

BY THE YEAR 2050



Of this population, the number of people with at least 1 chronic disease is estimated to increase by

99.5% ↑

The number of those with multiple comorbid conditions is estimated to increase by

~91% ↑

THE NUMBER OF PEOPLE WITH 1 OR MORE CHRONIC CONDITIONS IS EXPECTED TO INCREASE BY³³

NON-HISPANIC WHITE ADULTS AGED ≥50 YEARS

~99.5% ↑

NON-HISPANIC BLACK ADULTS AGED ≥50 YEARS

~85.6% ↑

HISPANIC ADULTS AGED ≥50 YEARS

~109.6% ↑

OTHER RACES (ADULTS AGED ≥50 YEARS)

~97.3% ↑

There is a need for broad protection against different strains of influenza virus in all adult patients, especially in older adults, and in individuals with certain chronic health conditions who are at higher risk for respiratory complications.

REF

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ABOUT FLUBLOK^{®7}

INDICATION

Flublok is a vaccine indicated for active immunization for the prevention of disease caused by influenza A virus subtypes and influenza type B virus represented by antigens contained in the vaccine. Flublok is approved for use in individuals 9 years of age and older.

CONTRAINDICATION

Do not administer Flublok to anyone with a history of severe allergic reactions (eg, anaphylaxis) to any component of the vaccine.

DOSING AND ADMINISTRATION



Flublok is administered as a single 0.5-mL dose for intramuscular injection



Prior to affixing the sterile needle for intramuscular administration, the prefilled syringe containing Flublok should be gently inverted. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. If either of these conditions exists, the vaccine should not be administered

STORAGE

- Flublok is supplied as a single-dose, prefilled, 0.5-mL syringe in a 10-syringe carton.
- It should be stored refrigerated between 2 °C and 8 °C (36 °F and 46 °F)
- Do not freeze. Discard if product has been frozen
- Protect syringes from light
- Do not use after expiration date shown on the label



WARNINGS AND PRECAUTIONS⁷

MANAGING ALLERGIC REACTIONS

Appropriate medical treatment must be immediately available to manage potential anaphylactic reactions following administration of Flublok.

GUILLAIN BARRÉ SYNDROME (GBS)

If GBS has occurred within 6 weeks of receipt of a prior influenza vaccine, the decision to give Flublok should be based on careful consideration of the potential benefits and risks.

The 1976 swine influenza vaccine was associated with an increased frequency of GBS. Evidence for a causal relation of GBS with other influenza vaccines is inconclusive; if an excess risk exists, it is probably slightly more than 1 additional case per 1 million persons vaccinated.

ALTERED IMMUNOCOMPETENCE

If Flublok is administered to immunocompromised individuals, including persons receiving immunosuppressive therapy, the immune response may be diminished.

LIMITATIONS OF VACCINE EFFECTIVENESS

Vaccination with Flublok may not protect all vaccine recipients.

SYNCOPE

Syncope (fainting) has been reported following vaccination with Flublok. Procedures should be in place to avoid injury from fainting.

MECHANISM OF ACTION⁷

Flublok contains recombinant HA proteins of the 3 strains of influenza virus specified by health authorities for inclusion in the annual seasonal vaccine. These proteins function as antigens that induce a humoral immune response, measured by hemagglutination inhibition antibody.



DESCRIPTION

Flublok is a sterile, clear, colorless injection containing recombinant HA proteins from 3 influenza viruses for intramuscular use. It contains purified HA proteins produced in a continuous insect cell line that is grown in a serum-free medium composed of chemically defined lipids, vitamins, amino acids, and mineral salts. Each of the 3 HAs is expressed in this cell line using a baculovirus vector, extracted from the cells, and further purified by column chromatography. The purified HAs are then blended and filled into single-dose syringes.⁷

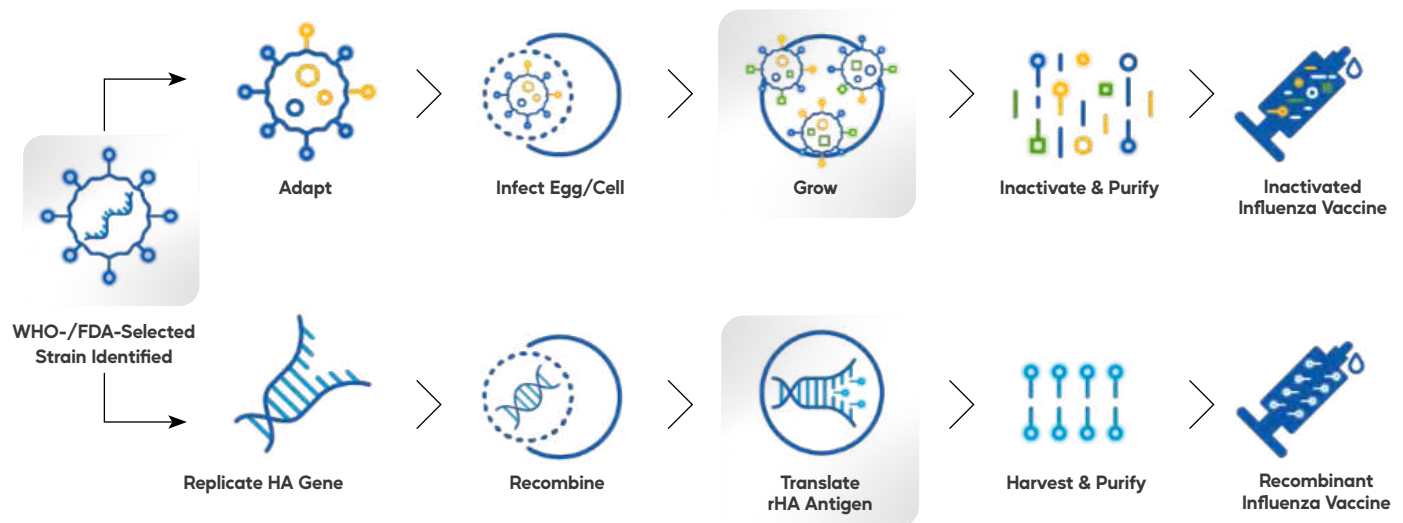
Flublok is standardized according to the United States Public Health Service requirements. Flublok contains no egg proteins, antibiotics, or preservatives. The single-dose, prefilled syringes contain no natural rubber latex.⁷

Flublok contains 3 times the HA antigen content of standard-dose flu vaccines, which has been associated with higher immunogenicity and relative vaccine efficacy when compared with standard-dose flu vaccines.^{34,a}

RECOMBINANT DNA TECHNOLOGY

Flublok uses recombinant DNA technology^{7b}

- Ensures identical antigenic match with WHO- and FDA-selected influenza strains⁸
- Avoids potential mutations in production that can reduce the protection of flu vaccines created with other technologies⁸
- Results in no potential for adaptation by eliminating the need to grow influenza virus in a cell or egg³⁴
- May lead to a broader immune response that may provide cross-protection, even in a mismatched season⁸



Graphical representation is for illustrative purposes only.

Abbreviation: rHA, recombinant influenza hemagglutinin.

^aFlublok contains 45 mcg of HA per strain vs 15 mcg of HA per strain in a standard-dose influenza vaccine.^{7,34}

^bFlublok is produced using a novel production platform in which recombinant HA is expressed in insect cells using a baculovirus expression vector system (BEVS).^{7,8} Recombinant HA antigens produced using BEVS have been shown to induce significantly higher levels of broadly cross-reactive antibodies against highly conserved regions of HA compared with egg-derived vaccines, which may provide the potential for protection against drift-variant influenza viruses.⁸



USE IN SPECIFIC POPULATIONS⁷

PREGNANCY

Pregnancy Exposure

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to Flublok. Healthcare providers are encouraged to enroll women who receive Flublok during pregnancy in Sanofi's vaccination pregnancy registry by calling 1-800-822-2463 or online by completing data collection form on <https://www.sanofivaccinespregnancyregistry.com/>.

Risk Summary

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies are 2% to 4% and 15% to 20%, respectively. Available data from a post-licensure observational, retrospective safety surveillance study showed no evidence of a vaccine-associated increase in the risk of major birth defects and miscarriages when Flublok Quadrivalent is administered during pregnancy.

A developmental study of Flublok has been performed in rats administered 0.5 mL (divided, a single human dose is 0.5 mL) of Flublok prior to mating and during gestation. This study revealed no evidence of harm to the fetus due to Flublok.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Pregnant women are at increased risk of complications associated with influenza infection compared with nonpregnant women. Pregnant women with influenza may be at increased risk for adverse pregnancy outcomes, including preterm labor and delivery.

LACTATION

Risk Summary

It is not known whether Flublok is excreted in human milk. Data are not available to assess the effects of Flublok on the breastfed infant or on milk production/excretion. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Flublok and any potential adverse effects on the breastfed child from Flublok or from the underlying maternal condition. For preventive vaccines, the underlying condition is susceptibility to disease prevented by the vaccine.

PEDIATRIC USE

Data from two randomized controlled trials, one in children 6 through 35 months and another in children 3 through 8 years of age, showed diminished hemagglutination inhibition (HI) antibody responses to Flublok or Flublok Quadrivalent, respectively, as compared to a U.S.-licensed influenza vaccine, strongly suggesting that Flublok and Flublok Quadrivalent would not be effective in children younger than 9 years of age.

GERIATRIC USE

Data from an efficacy study (Study 6), which included 1759 subjects aged ≥ 65 years and 525 subjects aged ≥ 75 years who received Flublok (quadrivalent), are insufficient to determine whether elderly subjects respond differently from younger subjects. Data for Flublok (quadrivalent) are relevant to Flublok (trivalent) because both vaccines are manufactured using the same process and have overlapping compositions.



CLINICAL STUDIES

The efficacy of Flublok (trivalent) and Flublok (quadrivalent) was evaluated in multiple clinical studies.⁷

Because both Flublok (trivalent) and Flublok (quadrivalent) are manufactured using the same process and have overlapping compositions, the efficacy of Flublok (quadrivalent) is relevant to Flublok (trivalent).⁷

SUMMARY OF CLINICAL STUDIES^{7,34}

	STUDY 1	STUDY 6
STUDY DESIGN	Randomized, observer-blind, placebo-controlled, multicenter trial	Randomized, observer-blind, active-controlled, multicenter trial
STUDY POPULATION	Adults aged 18 to 49 years	Adults aged ≥50 years
RANDOMIZATION	1:1 Flublok:saline placebo	1:1 Flublok (quadrivalent):United States-licensed quadrivalent inactivated influenza vaccine (comparator, Fluarix [quadrivalent standard-dose vaccine])
NUMBER OF SUBJECTS	N=4648 (Flublok n=2344, saline placebo n=2304)	N=8963 (Flublok [quadrivalent] n=4474, comparator n=4489)
PRIMARY ENDPOINT	Vaccine efficacy (VE) against CDC-defined influenza-like illness (CDC-ILI) ^a with a positive culture for an influenza virus strain represented in the vaccine	Relative vaccine efficacy (rVE) against influenza due to any PCR-confirmed circulating strains ^d
SECONDARY ENDPOINT	VE against any influenza-like illness (ILI) with a positive culture for an influenza virus strain represented in the vaccine ^{b,c}	rVE against influenza due to any culture-confirmed circulating strains ^d

Effectiveness in children and adolescents 9 years through 17 years of age is based on a comparison of immune response in this age group to adults 18 years through 49 years of age (Study 8; not shown).

Abbreviation: PCR, polymerase chain reaction.

^aCDC-ILI is defined as fever of ≥100 °F (oral) accompanied by cough, sore throat, or both on the same day or on consecutive days.⁷

^bILI was defined as having ≥2 of 3 symptoms (no specified duration) in the following categories: 1) fever ≥100 °F; 2) respiratory symptoms (cough, sore throat, or runny nose/stuffy nose); or 3) systemic symptoms (myalgias, arthralgias, headache, chills/sweats, or tiredness/malaise).⁷

^cAll culture-confirmed cases were considered, regardless of whether they qualified as CDC-ILI.⁷

^drVE was defined as 1 – (attack rate of Flublok [quadrivalent]/attack rate of comparator).⁷



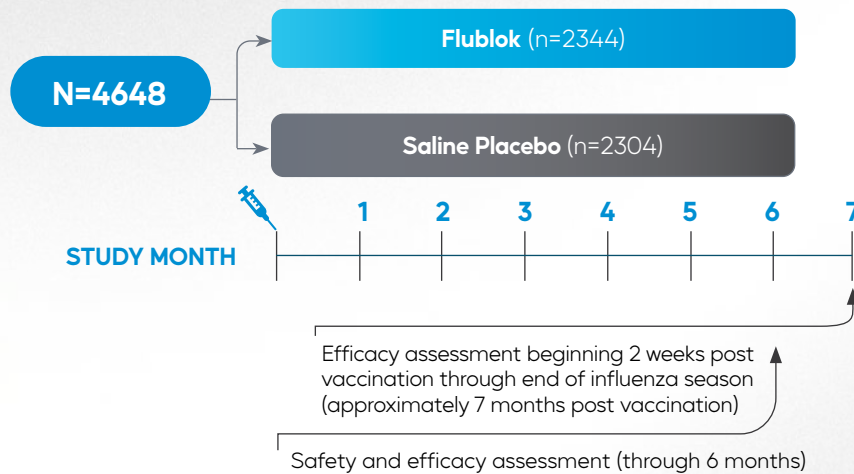
CLINICAL STUDIES (CONTINUED)

STUDY 1⁷

The efficacy of Flublok in protecting against influenza illness was evaluated in Study 1, a randomized, observer-blind, placebo-controlled, multicenter trial conducted in the United States during the 2007-2008 influenza season in adults aged 18 to 49 years.⁷

STUDY DESIGN

1:1 randomization
during 2007-2008
influenza season



PRIMARY ENDPOINT:

VE against CDC-ILI with a positive culture for an influenza virus strain represented in the vaccine^a

SECONDARY ENDPOINT:

VE against influenza due to any ILI with a positive culture for an influenza virus strain represented in the vaccine^{b,c}

^aCDC-ILI is defined as fever of ≥ 100 °F (oral) accompanied by cough, sore throat, or both on the same day or on consecutive days.⁷

^bILI was defined as having ≥ 2 of 3 symptoms (no specified duration) in the following categories: 1) fever ≥ 100 °F; 2) respiratory symptoms (cough, sore throat, or runny nose/stuffy nose); or 3) systemic symptoms (myalgias, arthralgias, headache, chills/sweats, or tiredness/malaise).⁷

^cAll culture-confirmed cases were considered, regardless of whether they qualified as CDC-ILI.⁷



CLINICAL STUDIES (CONTINUED)

EFFICACY RESULTS (STUDY 1)⁷

VE against antigenically matched culture-confirmed CDC-ILI could not be determined reliably because 96% of the influenza isolates obtained from subjects in Study 1 were not antigenically matched to the strains represented in the vaccine.

In an exploratory analysis of VE of Flublok against all strains, regardless of antigenic match, isolated from any subject with an ILI, Flublok showed the following efficacy estimates.

ANY CDC-ILI STRAIN:

44.6%
(95% CI: 18.8, 62.6)

FEWER INFLUENZA CASES AGAINST ANY CDC-ILI STRAIN, REGARDLESS OF MATCH TO THE VACCINE

ANY ILI STRAIN:

44.8%
(95% CI: 24.4, 60.0)

FEWER INFLUENZA CASES AGAINST ANY ILI STRAIN, REGARDLESS OF MATCH TO THE VACCINE



CLINICAL STUDIES (CONTINUED)

STUDY 1: VE AGAINST CULTURE-CONFIRMED INFLUENZA IN HEALTHY ADULTS AGED 18 TO 49 YEARS^{7a}

CASE DEFINITION	FLUBLOK (N=2344)		SALINE PLACEBO (N=2304)		FLUBLOK VE, % ^b	95% CI
	CASES, n	RATE, %	CASES, n	RATE, %		
POSITIVE CULTURE WITH A STRAIN REPRESENTED IN THE VACCINE						
CDC-ILI, ALL MATCHED STRAINS ^{c,d}	1	0.04	4	0.2	75.4	(-148.0, 99.5)
ANY ILI, ALL MATCHED STRAINS ^{e,f}	2	0.1	6	0.3	67.2	(-83.2, 96.8)
POSITIVE CULTURE WITH ANY STRAIN, REGARDLESS OF MATCH TO THE VACCINE						
CDC-ILI, ALL STRAINS ^{c,g}	44	1.9	78	3.4	44.6	(18.8, 62.6)
SUBTYPE A	26	1.1	56	2.4	54.4	(26.1, 72.5)
TYPE B	18	0.8	23	1.0	23.1	(-49.0, 60.9)
ANY ILI, ALL STRAINS ^e	64	2.7	114	4.9	44.8	(24.4, 60.0)
SUBTYPE A	41	1.7	79	3.4	49.0	(24.7, 65.9)
TYPE B	23	1.0	36	1.6	37.2	(-8.9, 64.5)

^aIn Study 1 (NCT00539981), VE analyses were conducted on the Total Vaccinated Cohort (all randomized subjects who received study vaccine according to the treatment actually received and who provided data). VE=1 – the ratio of Flublok/placebo infection rates.

^bDetermined under the assumption of Poisson event rates, according to Breslow and Day 1987.

^cMeets CDC-ILI, defined as a fever of >100 °F (oral) accompanied by cough and/or sore throat, on the same day or on consecutive days.

^dPrimary endpoint of trial.

^eAll culture-confirmed cases were considered, regardless of whether they qualified as CDC-ILI.

^fSecondary endpoint of trial.

^gExploratory (prespecified) endpoint of trial.



CLINICAL STUDIES (CONTINUED)

STUDY 6⁷

Study 6 evaluated the efficacy of Flublok (quadrivalent) in a randomized, observer-blind, active-controlled, multicenter trial conducted during the 2014-2015 influenza season in adults aged 50 years and older.^{7a}

STUDY DESIGN

1:1 randomization
during 2014-2015
influenza season

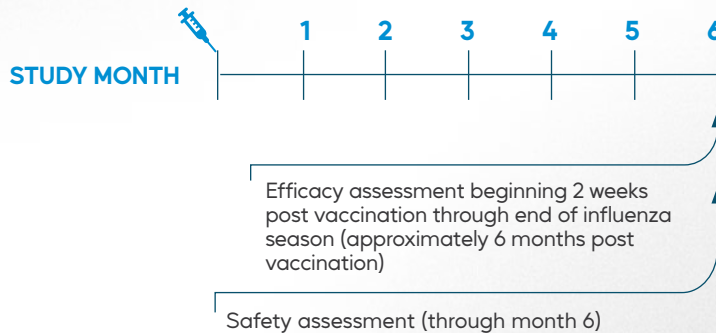
N=8963

Single dose of Flublok (quadrivalent)
(n=4474)

**Single dose of a US-licensed inactivated
quadrivalent vaccine (Fluarix [quadrivalent
standard-dose vaccine])** (n=4489)

PRIMARY ENDPOINT:
rVE against influenza
due to any PCR-
confirmed circulating
strains^b

SECONDARY ENDPOINT:
rVE against influenza
due to any culture-
confirmed circulating
strains^{7,34,b}



- At randomization, a total of 5186 (60%) subjects were aged 50 to 64 years and 3486 (40%) were aged ≥65 years.

^aCDC epidemiological data for the 2014-2015 influenza season indicated that influenza A(H3N2) viruses predominated and that most influenza A(H3N2) viruses were antigenically dissimilar while A(H1N1) and B viruses were antigenically similar to vaccine antigens.⁷

^brVE was defined as 1 - (attack rate Flublok [quadrivalent]/attack rate comparator).⁷



CLINICAL STUDIES (CONTINUED)

STUDY 6 EFFICACY RESULTS

PRIMARY ENDPOINT⁷



30% FEWER
INFLUENZA
CASES
(95% CI: 10, 47)

due to any PCR-confirmed
circulating strains

SECONDARY ENDPOINT^{7,34}



43% FEWER
INFLUENZA
CASES
(95% CI: 21, 59)

due to any culture-confirmed
circulating strains

Other secondary endpoints were evaluated, but are not included in this resource.^{7,34}



REAL-WORLD EVIDENCE

The real-world efficacy of Flublok (quadrivalent) was evaluated in a large retrospective study of the Medicare claims system,⁹ as well as in 2 studies of 2 large health systems in the United States: Kaiser Permanente Northern California (KPNC) and University of Pittsburgh Medical Center (UPMC).^{10,11}

The efficacy of Flublok (quadrivalent) is relevant to Flublok (trivalent) because both vaccines are manufactured using the same process and have overlapping compositions.⁷

SUMMARY OF REAL-WORLD STUDIES

	RETROSPECTIVE MEDICARE STUDY ⁹	KPNC STUDY ¹⁰	UPMC STUDY ¹¹
STUDY DESIGN	Retrospective observational cohort	Cluster-randomized observational study	Retrospective test-negative case-control study
STUDY POPULATION	Adults aged ≥65 years	Adults aged 18 to 64 years who received a Flublok (quadrivalent) or SD-IIV4 vaccine ^a	Hospitalized adults aged ≥18 years who had PCR testing for influenza
INFLUENZA SEASONS	2019-2020	2018-2019 and 2019-2020	2018-2019 and 2019-2020
# OF SUBJECTS	N=12,768,169 (HD-IIV3 n=7,177,250; allV3 n=2,564,628; IIV4 n=1,573,548; cIIV4 n=813,838; Flublok [quadrivalent]=638,905)	N=1,630,328 (Flublok [quadrivalent] n=632,962; SD-IIV4 n=997,366)	N=14,590 (Flublok [quadrivalent] n=3338; SD-IIV4 n=976; unvaccinated n=10,276)
PRIMARY ENDPOINTS	Influenza hospital encounters, which included inpatient hospitalizations and emergency department visits with an ICD-10-CM code for influenza	rVE of Flublok (quadrivalent) compared with SD-IIV4 against PCR-confirmed influenza in adults aged 50 to 64 years ^b	VE of Flublok (quadrivalent) and SD-IIV4 compared with no vaccination against influenza hospitalization in adults aged ≥18 years ^{c,d} rVE of Flublok (quadrivalent) compared with SD-IIV4 against influenza hospitalization in adults aged ≥18 years ^{c,e}
SECONDARY ENDPOINTS	Influenza inpatient hospitalizations only	rVE of Flublok (quadrivalent) compared with SD-IIV4 against PCR-confirmed influenza A and PCR-confirmed influenza B and hospitalization for PCR-confirmed influenza, community-acquired pneumonia (CAP), and cardiorespiratory events, including CAP, in adults aged 50 to 64 years ^b	Subgroup analyses of VE and rVE of Flublok (quadrivalent) and SD-IIV4 stratified by age (18 to 64 years and ≥65 years), sex, race, influenza season, and the presence of high-risk conditions

Abbreviations: allV3=egg-based adjuvanted trivalent; cIIV4=cell-cultured standard-dose quadrivalent; HD-IIV3=egg-based high-dose trivalent; ICD-10-CM, *International Classification of Diseases, Tenth Revision, Clinical Modification*; IIV4=egg-based standard-dose quadrivalent; SD-IIV4, quadrivalent standard-dose inactivated influenza vaccine.

^aThe primary and secondary endpoints were prespecified in adults aged 50 to 64 years. Outcomes in adults aged 18 to 49 years were considered exploratory.¹⁰

^brVE was defined as 1 – (hazard ratio of Flublok [quadrivalent] compared with SD-IIV4).¹⁰

^cSD-IIV4s included Afluria, Fluarix, FluLaval, Standard Dose Fluzone, and Flucelvax.¹¹

^dVE was defined as 1 – (adjusted odds ratio of influenza) x 100.¹¹

^erVE was defined as 1 – (the ratio of adjusted VE) x 100.¹¹



Please see full **Important Safety Information** on page 2.
Please click here for full **Prescribing Information**.



REAL-WORLD EVIDENCE (CONTINUED)

RETROSPECTIVE MEDICARE STUDY⁹

Real-world data from Medicare claims were used to analyze the rVE of US-licensed influenza vaccines in preventing hospital encounters among beneficiaries aged ≥65 years during the 2019-2020 season.

STUDY DESIGN

Design: Retrospective cohort

Population: 12.7 million adults aged ≥65 years.
HD-IIV3~7.2 million; aIIV3~2.6 million;
IIV4~1.6 million; cIIV4~0.8 million;
Flublok (quadrivalent)~0.6 million

Data Source: Medicare fee-for-service claims

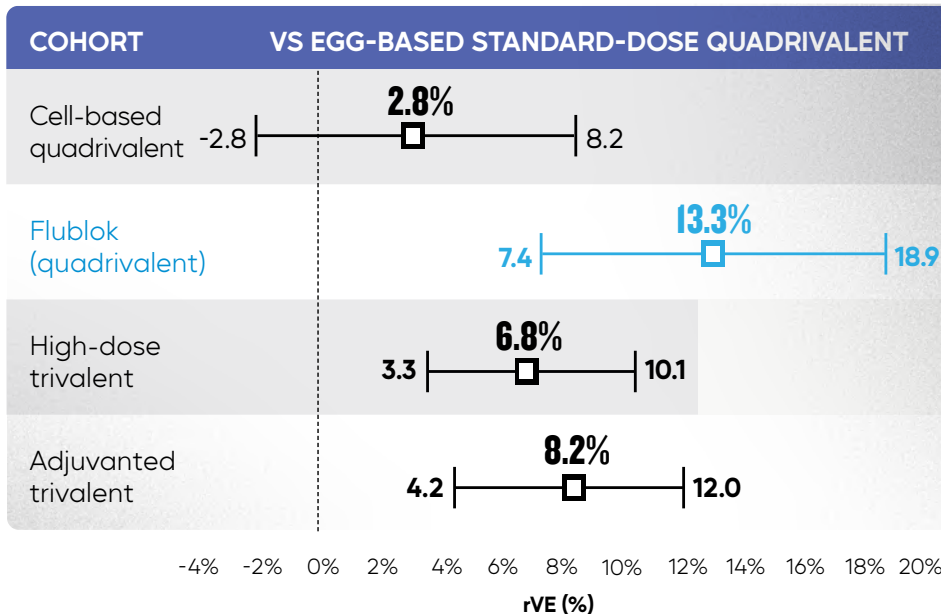
PRIMARY ENDPOINT:

Influenza hospital encounters, including inpatient hospitalizations and emergency department visits with an ICD-10-CM code for influenza

RESULTS⁹

2019-2020: Flublok (quadrivalent) was associated with significantly fewer influenza hospital encounters compared with standard-dose influenza vaccines

rVE AGAINST INFLUENZA HOSPITAL ENCOUNTERS (95% CI)^a



^aThe data shown are 1 of 3 primary analyses. Two additional primary analyses were conducted: 2 vaccine analyses, 1 comparing cIIV4 with IIV4 and 1 comparing Flublok (quadrivalent) with IIV4.

Study Limitations:

- Lack of access to virological case confirmation may have led to underestimation of the magnitude of differences
- Residual confounding by unmeasured covariates could have affected results

2019-2020 Season Characteristics:

- Influenza A(H1N1) and influenza B(Victoria) were predominating strains, with no significant circulation of influenza A(H3N2)
- An H1N1 strain with an amino acid change emerged late in the season and likely did not substantially affect the vaccine efficacy during the study period
- Trivalent vaccines contained the influenza B(Victoria) lineage



REAL-WORLD EVIDENCE (CONTINUED)

KAISER PERMANENTE NORTHERN CALIFORNIA (KPNC) STUDY¹⁰

The real-world efficacy of Flublok (quadrivalent) compared with SD-IIV4 vaccines for protecting against influenza illness was evaluated in a cluster-randomized observational study in adults aged 18 to 64 years conducted in the KPNC health system.

STUDY DESIGN

Patient sample selection: The study included 1,630,328 KPNC members aged 18 to 64 years who had received a Flublok (quadrivalent) or SD-IIV4 vaccination as part of routine clinical care during the 2 influenza seasons from 2018 to 2020

Randomization: Within each KPNC service area, facilities of similar size were randomly assigned to Block A or Block B. Block A began vaccination with SD-IIV4 and Block B began with Flublok (quadrivalent). Each facility then alternated the administrated vaccine weekly until the end of the season

PRIMARY ENDPOINT:

rVE of Flublok (quadrivalent) compared with SD-IIV4 against PCR-confirmed influenza in adults aged 50 to 64 years


SECONDARY ENDPOINT:

rVE Flublok (quadrivalent) compared with SD-IIV4 against PCR-confirmed influenza A and PCR-confirmed influenza B and hospitalization for PCR-confirmed influenza, CAP, and cardiorespiratory events, including CAP, in adults aged 50 to 64 years

EFFICACY RESULTS¹⁰

PRIMARY ENDPOINT

In adults aged 50 to 64 years, Flublok (quadrivalent) was associated with greater protection than SD-IIV4, with

 **15.3%** **FEWER INFLUENZA CASES**
(95% CI: 5.9-23.8)

PCR-CONFIRMED INFLUENZA (ALL)

	FLUBLOK (QUADRIVALENT) n (CASES PER 1000) N=279,400	SD-IIV4 VACCINE n (CASES PER 1000) N=395,852	ESTIMATED rVE % (95% CI)
PCR-confirmed influenza (all)	559 (2.00)	925 (2.34)	15.3 (5.9-23.8)

Note: Bolding indicates statistical significance.



REAL-WORLD EVIDENCE (CONTINUED)

PCR-CONFIRMED INFLUENZA IN ADULTS AGED 50 TO 64 YEARS¹⁰
VACCINE EFFECTIVENESS IN ADULTS AGED 50 TO 64 YEARS^a

OTHER SECONDARY ENDPOINTS	FLUBLOK (QUADRIVALENT) n (CASES PER 1000) N=279,400	SD-IIV4 n (CASES PER 1000) N=395,852	UNADJUSTED RATE RATIO	ADJUSTED HAZARD RATIO (95% CI) ^b	FLUBLOK (QUADRIVALENT) rVE (95% CI) ^c
PCR-CONFIRMED INFLUENZA A	522 (1.87)	862 (2.18)	0.86	0.84 (0.76 to 0.94)	15.7 (6.0 to 24.5)
PCR-CONFIRMED INFLUENZA B	37 (0.13)	64 (0.16)	0.82	0.90 (0.60 to 1.34)	10.3 (-33.9 to 39.9)
HOSPITALIZATION FOR PCR-CONFIRMED INFLUENZA	95 (0.34)	153 (0.39)	0.88	0.84 (0.65 to 1.09)	15.9 (-9.2 to 35.2)
HOSPITALIZATION FOR CAP	106 (0.38)	183 (0.46)	0.82	0.83 (0.66 to 1.06)	16.7 (-5.6 to 34.4)
HOSPITALIZATION FOR CARDIORESPIRATORY EVENT	631 (2.26)	890 (2.25)	1.004	0.98 (0.88 to 1.08)	2.4 (-8.1 to 11.9)

- Post hoc analysis combining hospitalization for PCR-confirmed influenza and hospitalization for CAP yielded an rVE of 19.7% (95% CI, 2.8-33.7)
- Flublok (quadrivalent) was not more protective than SD-IIV4 against influenza B, or against hospitalization for PCR-confirmed influenza, CAP, or cardiorespiratory events, in adults aged 50 to 64 years

Note: Bolding indicates statistical significance.

^aThe primary and secondary endpoints were prespecified in adults aged 50 to 64 years. Outcomes in adults aged 18 to 49 years were considered exploratory.

^bHazard ratios were adjusted for age, age squared, sex, and race or ethnic group after weighting with stabilized facility-specific propensity scores.

^crVE was defined as 1 – (hazard ratio of Flublok [quadrivalent] compared with SD-IIV4).

Study Limitations¹⁰:

- Compliance with the weekly assigned vaccine schedule varied from time to time due to logistical constraints
- Data were limited to 2 influenza seasons, and rVE may vary across seasons based on the vaccine vs the circulating strain
- Study had limited power to detect a clinically meaningful benefit of Flublok (quadrivalent) vs SD-IIV4 with respect to several less frequent outcomes, such as hospitalized PCR-confirmed influenza
- Although KPNC has a large geographically, racially, and ethnically diverse population, it may not be representative of other populations

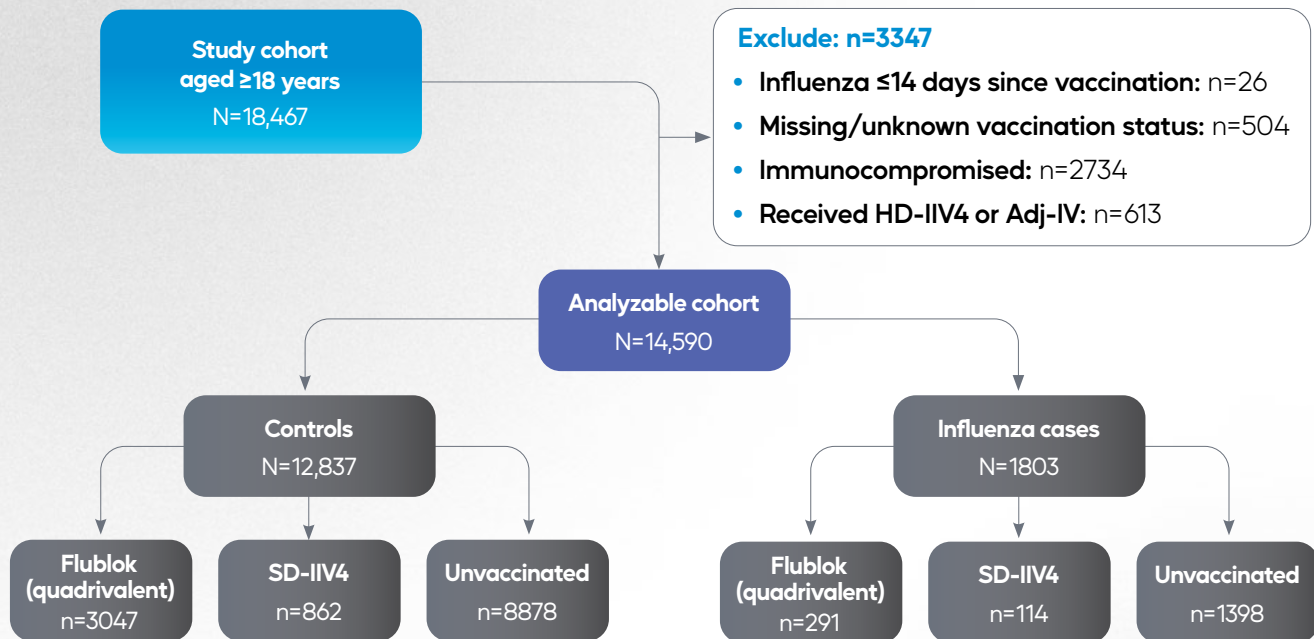


REAL-WORLD EVIDENCE (CONTINUED)

UNIVERSITY OF PITTSBURGH MEDICAL CENTER (UPMC) STUDY¹¹

The real-world efficacy of Flublok (quadrivalent) compared with SD-IIV4 vaccines for protecting against hospitalization for influenza was evaluated in a test-negative case-control study of adults aged ≥18 years conducted in the UPMC health system.^a

STUDY DESIGN



Patient sample selection: The study included all patients aged ≥18 years who were hospitalized in the UPMC system and had a PCR test for influenza. Those who tested positive for influenza were considered influenza cases and those who tested negative were considered controls, regardless of any other viral infection

^aPatients were aged ≥18 years on August 1 of each influenza season and were tested for influenza between November 1, 2018, and April 30, 2020.

^bThe sample size of SD-IIV4 recipients may have been inadequate to estimate meaningful rVE for subgroups.

PRIMARY ENDPOINTS:

- VE of Flublok (quadrivalent) and SD-IIV4 compared with no vaccination against influenza hospitalization in adults aged ≥18 years
- rVE of Flublok (quadrivalent) compared with SD-IIV4 against influenza hospitalization in adults aged ≥18 years

SECONDARY ENDPOINT:

Subgroup analyses of VE and rVE of Flublok (quadrivalent) and SD-IIV4 against influenza by age, race, sex, season, and high-risk conditions^b



REAL-WORLD EVIDENCE (CONTINUED)

EFFICACY RESULTS¹¹

- Flublok (quadrivalent) was more protective than SD-IIV4 against influenza hospitalizations when adjusted for propensity scores with IPWs. The rVE was not significant when adjusted using *a priori* variables

 **31%** **FEWER INFLUENZA HOSPITALIZATIONS IN ADULTS AGED ≥18 YEARS**
(95% CI: 11, 46)

- Flublok (quadrivalent) and SD-IIV4 were more protective against influenza hospitalizations compared with no vaccination (Flublok [quadrivalent] VE: 36%, 95% CI: 27, 45; SD-IIV4 VE: 24%, 95% CI: 6, 38)

VE AND rVE IN HOSPITALIZED ADULTS AGED ≥18 YEARS¹¹

GROUP	VE FLUBLOK (QUADRIVALENT) VS NO VACCINATION % (95% CI)	VE SD-IIV4 ^a VS NO VACCINATION % (95% CI)	rVE FLUBLOK (QUADRIVALENT) VS SD-IIV4 ^a % (95% CI) ADJUSTED USING IPW
OVERALL	36 (27, 45)	24 (6, 38)	31 (11, 46)
FEMALE SEX	40 (28, 50)	20 (-4, 39)	37 (13, 54)
MALE SEX	31 (16, 44)	28 (0, 49)	23 (-14, 48)
18-64 YEARS	47 (35, 57)	27 (8, 42)	28 (3, 46)
≥65 YEARS	27 (12, 39)	9 (-42, 42)	17 (-36, 48)
HIGH-RISK CONDITION	30 (19, 40)	21 (-2, 39)	20 (-7, 40)
NO HIGH-RISK CONDITION	67 (50, 78)	27 (-4, 49)	60 (29, 78)
2018-2019 SEASON	31 (15, 45)	20 (-6, 41)	28 (-5, 50)
2019-2020 SEASON	40 (29, 50)	26 (1, 45)	30 (1, 50)

Note: Bolding indicates statistical significance.

^aSD-IIV4: Afluria, Fluarix, FluLaval, Fluzone, and Flucelvax.

Abbreviation: IPW, inverse probability weight.



REAL-WORLD EVIDENCE (CONTINUED)

Study Strengths and Limitations¹¹:

- The demographics of the study population were representative of the adult population of Allegheny County, with 79% being White and 51% being female, which contributes to generalizability
- The UPMC hospitals are part of an integrated health system, with regular uploads of vaccination data from the state immunization registry; vaccination status was verified through the state registry with a specific data request
- Although the electronic medical record (EMR) system of UPMC hospitals is robust, if vaccinations were not captured in the EMRs or state registry, they were classified as unvaccinated
- Because data focused on hospitalizations, there may have been milder cases of influenza that were not captured in the EMRs because they didn't require medical care
- There is the possibility of selection bias among those who received influenza testing; for instance, clinicians might preferentially test unvaccinated subjects, which would increase the proportion of unvaccinated cases



FLUBLOK SAFETY WAS EVALUATED IN MORE THAN 14,000 PREGNANT PEOPLE⁷

THE CDC RECOMMENDS FLU VACCINATION FOR PREGNANT PEOPLE TO HELP PROTECT THEMSELVES AND THEIR BABIES³⁴

Pregnant people are at higher risk of severe flu-related illness and hospitalization.³

Pregnant people who receive a flu vaccination

- Have 40% lower risk of hospitalization with flu^{36,a}
- Help protect their babies from flu-related illness and hospitalization when they are too young to be immunized³⁴

RWE STUDY DESIGN

This was an observational, retrospective safety surveillance study of Flublok Quadrivalent in 14,981 pregnant individuals across Northern Hemisphere influenza seasons 2018-2019 and 2019-2020.^{7,b,c,d}

This study represents the largest population of pregnant people to be included in the prescribing information for any FDA-approved flu vaccine.^{7,37,38}

OUTCOMES

There was **no evidence of a vaccine-associated increase in the risk of major birth defects and miscarriages** when Flublok was administered during pregnancy.^{7,d}

^aRetrospective test negative design study, 2010–2016, that evaluated adjusted overall influenza vaccine efficacy against influenza-associated hospitalization during pregnancy (N=1030).³⁶

^bPatients, including those with chronic conditions, were exposed to Flublok Quadrivalent during the 28 days prior to conception or across all stages of pregnancy.⁷

^cPrespecified outcomes included spontaneous abortion and congenital/fetal anomalies. Data were not collected on ectopic pregnancy or elective terminations.⁷

^dThe data for Flublok (quadrivalent) are relevant to Flublok (trivalent) because both vaccines are manufactured using the same process and have overlapping compositions.⁷



SAFETY PROFILE IN ADULTS⁷

The safety of Flublok (trivalent) was analyzed in 4 randomized, placebo- or active-controlled clinical trials

- **Study 1** (NCT00539981) included 4648 subjects aged 18 to 49 years randomized to receive Flublok (n=2344) or placebo (n=2304)
- **Study 2** (NCT00539864) included 602 subjects aged 50 to 64 years randomized to receive Flublok (n=300) or another US-licensed trivalent influenza vaccine (Fluzone, manufactured by Sanofi) as an active control (n=302)
- **Study 3** (NCT00395174) included 869 subjects aged ≥ 65 years randomized to receive Flublok (n=436) or another US-licensed trivalent influenza vaccine (Fluzone) as an active control (n=433)
- **Study 4** (NCT01825200) included 2627 subjects aged ≥ 50 years randomized to receive Flublok (n=1314) or another US-licensed trivalent influenza vaccine (Afluria, manufactured by bioCSL Pty Ltd.) as an active control (n=1313)
 - Among subjects aged 50 to 64 years, 672 received Flublok and 665 received Afluria
 - Among subjects aged 65 years and older, 642 received Flublok and 648 received Afluria

The safety experience with Flublok (quadrivalent) is relevant to Flublok (trivalent) because both vaccines are manufactured using the same process and have overlapping compositions.

Flublok (quadrivalent) has been administered to and safety data collected from 4328 adults aged ≥ 50 years (Study 6) and 998 adults aged 18 to 49 years (Study 7). SAEs were collected for 6 months post vaccination via clinic visit or remote contact.

- **Study 6** (NCT02285998) enrolled subjects aged ≥ 50 years randomized to receive Flublok (quadrivalent) or comparator (Fluarix [quadrivalent standard-dose vaccine], manufactured by GlaxoSmithKline) as an active control. The safety analysis population included 4328 Flublok (quadrivalent) recipients and 4344 comparator vaccine recipients
- **Study 7** (NCT02290509) enrolled subjects aged 18 to 49 years randomized to receive Flublok (quadrivalent) or a comparator inactivated influenza vaccine (Fluarix [quadrivalent standard-dose vaccine]). The safety analysis population included 998 recipients of Flublok (quadrivalent) and 332 comparator vaccine recipients



SAFETY PROFILE IN ADULTS (CONTINUED)⁷

SAFETY IN ADULTS AGED 18 TO 49 YEARS

In adults aged 18 to 49 years, the most common ($\geq 10\%$) injection-site adverse reaction was pain (37%); the most common ($\geq 10\%$) solicited systemic adverse reactions were headache (15%), fatigue (15%), and muscle pain (11%).

FREQUENCY OF SOLICITED LOCAL INJECTION SITE ADVERSE REACTIONS AND SYSTEMIC ADVERSE REACTIONS WITHIN 7 DAYS OF ADMINISTRATION OF FLUBLOK OR PLACEBO IN ADULTS AGED 18 TO 49 YEARS, STUDY 1, TOTAL VACCINATED COHORT^{a-c}

	FLUBLOK n=2272			PLACEBO n=2231		
	Any	Moderate ^d	Severe ^d	Any	Moderate ^d	Severe ^d
LOCAL	%			%		
Pain	37	2	<1	8	<1	<1
Redness	4	<1	<1	2	<1	<1
Swelling	3	<1	<1	2	<1	<1
Bruising	3	<1	<1	3	<1	<1
SYSTEMIC	%			%		
Headache	15	3	<1	16	3	<1
Fatigue	15	3	<1	14	3	<1
Muscle Pain	11	2	<1	7	<1	<1
Nausea	6	1	<1	5	1	<1
Joint Pain	4	<1	<1	4	<1	<1
Chills	3	<1	<1	3	<1	<1
Fever ^e	<1	<1	<1	<1	<1	<1

Note: Data based on the most severe response reported by subjects. Results $\geq 1\%$ reported to nearest whole percent; results >0 but $<1\%$ reported as $<1\%$.

^aTotal Vaccinated Cohort is defined as all randomized subjects who received study vaccine according to the treatment actually received and who provided data.

^bStudy 1 is registered as NCT00539981 under the National Clinical Trials registry.

^cDenominators for Study 1: The total number of enrolled, randomized, and vaccinated subjects was 2344 in the Flublok group and 2304 in the placebo group. For all categories except fever, the number of subjects with missing values was 72 in the Flublok group and 73 in the placebo group; thus, these denominators are 2272 and 2231, respectively. For fever, 89 Flublok recipients and 104 placebo recipients were missing data, making these denominators 2255 and 2200, respectively.

^dModerate=prevented a significant part of usual activities; severe=prevented most or all of normal activities or had to see a doctor for prescription medicine.

^eFever defined as ≥ 100.4 °F (38 °C). Mild (≥ 100.4 °F to <101.1 °F); moderate (≥ 101.2 °F to <102.2 °F); severe (≥ 102.2 °F).



SAFETY PROFILE IN ADULTS (CONTINUED)⁷

SAFETY IN ADULTS AGED 50 TO 64 YEARS

In adults aged 50 to 64 years, the most common ($\geq 10\%$) injection site adverse reaction was pain (32%); the most common ($\geq 10\%$) solicited systemic adverse reactions were headache (17%), fatigue (13%), and muscle pain (11%). Most adverse reactions were mild in severity.

FREQUENCY OF SOLICITED LOCAL INJECTION SITE ADVERSE REACTIONS AND SYSTEMIC ADVERSE REACTIONS WITHIN 7 DAYS OF ADMINISTRATION OF FLUBLOK OR COMPARATOR IN ADULTS AGED 50 TO 64 YEARS, STUDIES 2 AND 4, TOTAL VACCINATED COHORT^{a,b}

	FLUBLOK n=972			PLACEBO ^b n=967		
	Any	Moderate ^c	Severe ^c	Any	Moderate ^c	Severe ^c
LOCAL	%			%		
Pain	32	2	<1	37	<1	0
Firmness/Swelling	7	2	<1	6	1	<1
Redness	6	2	<1	5	1	<1
SYSTEMIC	%			%		
Headache	17	4	<1	16	3	<1
Fatigue	13	3	<1	17	3	<1
Muscle Pain	11	2	<1	11	2	<1
Nausea	8	2	<1	8	2	<1
Joint Pain	6	1	0	5	<1	<1
Chills	5	1	0	4	<1	<1
Fever ^e	<1	<1	<1	<1	0	0

Note: Data based on the most severe response reported by subjects. Results $\geq 1\%$ reported to nearest whole percent; results >0 but $<1\%$ reported as $<1\%$.
^aTotal Vaccinated Cohort is defined as all randomized subjects who received study vaccine according to the treatment actually received and who provided data.

^bPooled data from Studies 2 and 4. For Studies 2 and 4, the US-licensed IIV3 comparators were Fluzone and Afluria, respectively. Studies 2 and 4 are registered as NCT00539864 and NCT01825200, respectively, under the National Clinical Trials registry.

^cModerate=prevented a significant part of usual activities; severe=prevented most or all of normal activities, or had to see a doctor for prescription medicine.

^eFever defined as ≥ 100.4 °F (38 °C). Mild (≥ 100.4 °F to <101.1 °F); moderate (≥ 101.2 °F to <102.2 °F); severe (≥ 102.2 °F). For fever, 12 Flublok recipients and 5 IIV3 recipients were missing data, making these denominators 964 and 962, respectively.



SAFETY PROFILE IN ADULTS (CONTINUED)⁷

SAFETY IN ADULTS AGED 65 YEARS AND OLDER

In adults aged 65 years and older, the most common ($\geq 10\%$) injection site adverse reaction was pain (19%); the most common ($\geq 10\%$) solicited systemic adverse reactions were fatigue (13%) and headache (10%). Most adverse reactions were mild in severity.

FREQUENCY OF SOLICITED LOCAL INJECTION SITE ADVERSE REACTIONS AND SYSTEMIC ADVERSE REACTIONS WITHIN 7 DAYS OF ADMINISTRATION OF FLUBLOK OR COMPARATOR IN ADULTS AGED ≥ 65 YEARS, STUDIES 3 AND 4, TOTAL VACCINATED COHORT^{a,b}

	FLUBLOK n=1078			PLACEBO ^b n=1081		
	Any	Moderate ^c	Severe ^c	Any	Moderate ^c	Severe ^c
LOCAL	%			%		
Pain	19	<1	<1	20	<1	<1
Redness	7	1	<1	7	1	1
Firmness/Swelling	7	2	<1	7	<1	<1
SYSTEMIC	%			%		
Fatigue	13	3	<1	15	2	<1
Headache	10	<1	<1	9	1	<1
Muscle Pain	8	2	<1	8	1	<1
Joint Pain	6	1	<1	6	1	<1
Shivers/Chills	5	<1	<1	5	<1	<1
Nausea	4	<1	<1	3	<1	<1
Fever ^d	3	<1	<1	2	0	0

Note: Data based on the most severe response reported by subjects. Results $\geq 1\%$ reported to nearest whole percent; results >0 but $<1\%$ reported as $<1\%$.
^aTotal Vaccinated Cohort is defined as all randomized subjects who received study vaccine according to the treatment actually received and who provided data.

^bPooled data from Studies 3 and 4. For Studies 3 and 4, the US-licensed IIV3 comparators were Fluzone and Afluria, respectively. Studies 3 and 4 are registered as NCT00395174 and NCT01825200, respectively, under the National Clinical Trials registry.

^cModerate=prevented a significant part of usual activities; severe=prevented most or all of normal activities, or had to see a doctor for prescription medicine.

^dFever defined as ≥ 100.4 °F (38 °C). Mild (≥ 100.4 °F to <101.1 °F); moderate (≥ 101.2 °F to <102.2 °F); severe (≥ 102.2 °F).



SUMMARY

- Some groups of people are at higher risk for other complications that can result in hospitalization³
 - There is a need for broad protection against different strains of influenza virus in all adult patients, especially in older adults and in individuals with certain chronic health conditions who are at higher risk for respiratory complications
- Flublok is a single-dose vaccine containing recombinant HA proteins from the 3 strains of influenza virus specified by health authorities for inclusion in the annual seasonal vaccine⁷
 - Recombinant DNA technology ensures identical antigenic match with WHO- and FDA-selected influenza strains and avoids potential mutations in production that can reduce the protection of flu vaccines created with other technologies.⁸ This results in no potential for adaptation because it eliminates the need to grow influenza virus in a cell or egg³⁴
 - Recombinant DNA technology may lead to a broader immune response that may provide cross-protection, even in a mismatched season⁸
- The VE and rVE of Flublok have been evaluated in multiple clinical studies⁷
 - In Study 1, an exploratory analysis, Flublok (trivalent) showed 44.6% fewer influenza cases against any CDC-defined ILI strain, regardless of match to the vaccine (95% CI: 18.8, 62.6) and 44.8% fewer influenza cases against any ILI strain, regardless of match to the vaccine (95% CI: 24.4, 60.0) compared with placebo^a
 - Given 96% of the influenza isolates obtained were not antigenically matched to the strains represented in the vaccine, the primary endpoint against antigenically matched strains was not able to be obtained
 - In Study 6, Flublok (quadrivalent) resulted in 30% fewer influenza cases due to any PCR-confirmed circulating strain compared with a US-licensed comparator (95% CI: 10, 47)^b
- The real-world efficacy of Flublok (quadrivalent) was assessed in a retrospective study using a Medicare claims database, and in 2 studies of 2 large health systems in the United States⁹⁻¹¹
 - In a retrospective study, Flublok (quadrivalent) was associated with significantly fewer influenza hospital encounters compared with standard-dose influenza vaccines^{9c}
 - In a study from KPNC, Flublok (quadrivalent) was associated with being more protective than SD-IIV4 in adults aged 50 to 64 years^{10,d}
 - In a study from UPMC, Flublok (quadrivalent) and SD-IIV4 were associated with being more protective against influenza compared with no vaccination. Flublok (quadrivalent) was more protective than SD-IIV4 against influenza when adjusted using inverse probability weighting^{11,e}
- In adults, Flublok was generally well tolerated and had a similar safety profile to placebo and the comparator vaccines across all age groups in clinical trials⁷
 - The most common injection-site adverse reaction was pain and the most common solicited systemic adverse reactions were headache, fatigue, and muscle pain

^aStudy 1 was a randomized, observer-blind, placebo-controlled multicenter trial conducted in the United States during the 2007-2008 influenza season in 4648 adults aged 18 to 49 years comparing the efficacy of Flublok (trivalent formulation) (n=2344) with placebo (n=2304). The primary endpoint was VE against CDC-ILI with a positive culture for an influenza virus strain represented in the vaccine.⁷

^bStudy 6 was a randomized, observer-blind, active-controlled, multicenter trial conducted during the 2014-2015 influenza season in 8963 adults aged ≥50 years comparing the efficacy of Flublok (quadrivalent) (n=4474) vs a US-licensed inactivated quadrivalent comparator (Fluarix [quadrivalent standard-dose vaccine]; n=4489). The primary endpoint was rVE against influenza due to any PCR-confirmed circulating strains.⁷

^cReal-world data from Medicare claims were used to analyze the rVE of US-licensed influenza vaccines in preventing hospital encounters among 12.7 million beneficiaries aged ≥65 years during the 2019-2020 season. The primary endpoint was influenza hospital encounters, including inpatient hospitalizations and emergency department visits with an ICD-10-CM code for influenza.⁹

^dA cluster-randomized real-world observational study of 1,630,328 adults aged 18 to 64 years conducted in the KPNC health system compared the efficacy of Flublok (quadrivalent) with SD-IIV4 vaccines for protecting against influenza illness was evaluated. The primary endpoint was rVE of Flublok (quadrivalent) compared with SD-IIV4 against PCR-confirmed influenza.¹⁰

^eA retrospective test-negative case-control real-world study of adults aged 18 years and older was conducted in the UPMC health system to compare the VE of Flublok (quadrivalent) and SD-IIV4 compared with no vaccination against influenza hospitalization and the rVE of Flublok (quadrivalent) compared with SD-IIV4 against influenza hospitalization.¹¹



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CODING AND BILLING INFORMATION FOR FLUBLOK®

This coding information is provided for informational purposes only and does not constitute legal or reimbursement advice. It is not intended to substitute for the physician's independent diagnosis or treatment of each patient. The information contained herein is gathered from various resources and is subject to change. Providers are solely responsible for the accuracy of all coding and claims submitted for reimbursement to any third-party payer.

	CODE	DESCRIPTION
PRODUCT CPT CODE ¹	90673	Influenza virus vaccine, trivalent (RIV3), derived from recombinant DNA, hemagglutinin (HA) protein only, preservative and antibiotic free, for intramuscular use
ADMINISTRATION ¹	90460 (1 unit) OR 90471 (1 unit) OR 90472 (1 unit) OR G0008 (1 unit, Medicare and Tricare Requirement)	Administration of influenza virus vaccine
NDC: CARTON ²	49281-725-10	Carton of 10 single-dose, 0.5 mL prefilled syringes
NDC: UNIT OF USE ²	49281-725-88	Single-dose, 0.5 mL prefilled syringe
CVX CODE ³	155	Influenza, recombinant, trivalent, injectable, preservative free
TYPICAL ICD-10 CODE ¹	Z23	Encounter for immunization

When NDCs are required by the payer, use the N4 qualifier, followed by the correct 11-digit Carton NDC or Unit of Use NDC and the unit of measure in the actual number of milliliters administered (eg, ML0.5). To convert the NDC to the required 11-digit format, add a leading zero in the middle section of numbers (eg, 49281-725-10 → 49281-0725-10).⁴

Abbreviations: CPT, Current Procedural Terminology®; CVX, Vaccine Administration; HCPCS, Healthcare Common Procedure Coding System; ICD-10-CM, *International Classification of Diseases, Tenth Revision, Clinical Modification*; NDC, National Drug Code.



INDICATION AND IMPORTANT SAFETY INFORMATION FOR FLUBLOK[®] (INFLUENZA VACCINE)

FLUBLOK[®] (INFLUENZA VACCINE)

Flublok is a vaccine indicated for active immunization for the prevention of disease caused by influenza A virus subtypes and influenza type B virus represented by antigens contained in the vaccine. Flublok is approved for use in individuals 9 years of age and older.

IMPORTANT SAFETY INFORMATION FOR FLUBLOK[®] (INFLUENZA VACCINE)

Do not administer Flublok to anyone with a history of severe allergic reactions (e.g., anaphylaxis) to any component of the vaccine.

Appropriate medical treatment must be immediately available to manage potential anaphylactic reactions following administration of Flublok.

If Guillain-Barré syndrome has occurred within 6 weeks of receipt of a prior influenza vaccine, the decision to give Flublok should be based on careful consideration of the potential benefits and risks.

If Flublok is administered to immunocompromised persons, including those receiving immunosuppressive therapy, the immune response may be diminished.

Vaccination with Flublok may not protect all recipients.

Syncope (fainting) has been reported following vaccination with Flublok. Procedures should be in place to avoid injury from fainting.

In children 9 through 17 years of age who received Flublok Quadrivalent, the most common solicited injection-site adverse reaction was pain; the most common solicited systemic adverse reactions were myalgia, headache, and malaise. In adults 18 through 64 years of age who received Flublok, the most common injection site adverse reaction was pain; the most common solicited systemic adverse reactions were headache, fatigue, and myalgia. In adults 65 years of age and older who received Flublok, the most common injection-site adverse reaction was pain; the most common solicited systemic adverse reactions were fatigue and headache. Other adverse reactions may occur.



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ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES (ACIP) RECOMMENDATIONS¹

The ACIP recommends vaccination with a licensed, age-appropriate seasonal influenza vaccine for all persons aged ≥ 6 months who do not have contraindications.

For the 2024-2025 influenza season, the ACIP makes no preferential recommendation for a specific vaccine when multiple licensed, recommended, and age-appropriate vaccines are available, except for adults aged ≥ 65 years. The ACIP recommends adults in this age group preferentially receive any of the higher-dose or adjuvanted influenza vaccines



- High-dose inactivated influenza vaccine (HD-IIV3)
- Recombinant influenza vaccine (RIV3)
- Adjuvanted inactivated influenza vaccine (aIIV3)

If none of these 3 vaccines are available at a vaccination opportunity, then any other age-appropriate influenza vaccine should be used.

Vaccination should ideally occur during September or October, but should continue to be offered throughout the season as long as influenza viruses are circulating and unexpired vaccine is available.

While influenza vaccines may be available earlier, it is recommended that most adults, especially those aged ≥ 65 years, and pregnant persons in their first or second trimester avoid vaccination in July or August unless there is concern that vaccination later in the season may not be possible. Vaccination during July or August can be considered for pregnant persons who are in the third trimester if vaccine is available.



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If Flublok is administered to immunocompromised persons, including those receiving immunosuppressive therapy, the immune response may be diminished.

Vaccination with Flublok may not protect all recipients.

Syncope (fainting) has been reported following vaccination with Flublok. Procedures should be in place to avoid injury from fainting.

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Flublok[®]

Influenza Vaccine