Supplementary Materials

Superior effectiveness and estimated public health impact of cell- versus egg-based influenza vaccines in children and adults during the US 2023–2024 season

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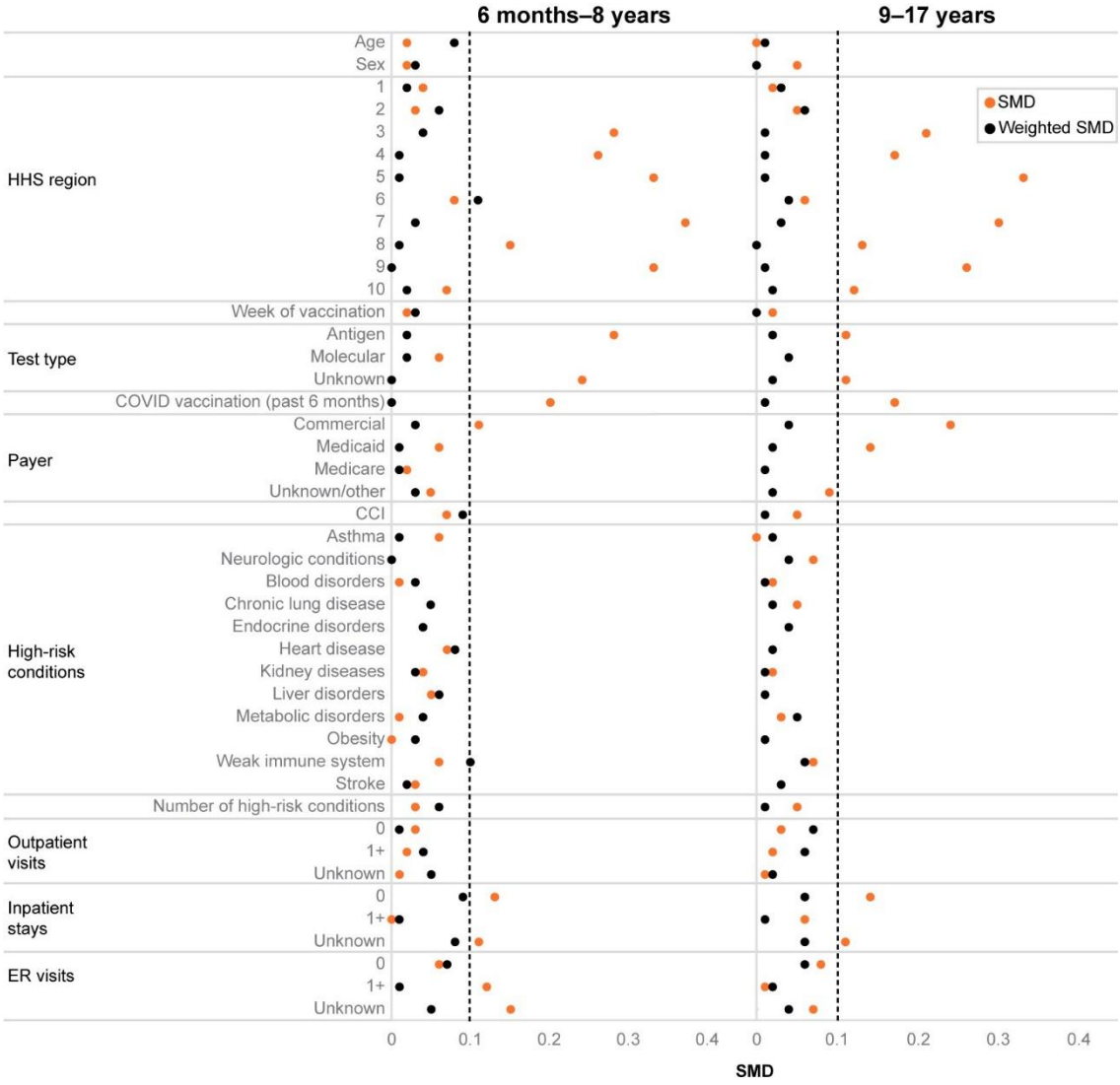
Supplementary Figure 1. Covariate balance between vaccine groups (QIVc and QIVe) among test-negative controls, before and after weighting, in patients aged 6 months–8 years and patients aged 9–17 years (2023–2024 influenza season in the US)



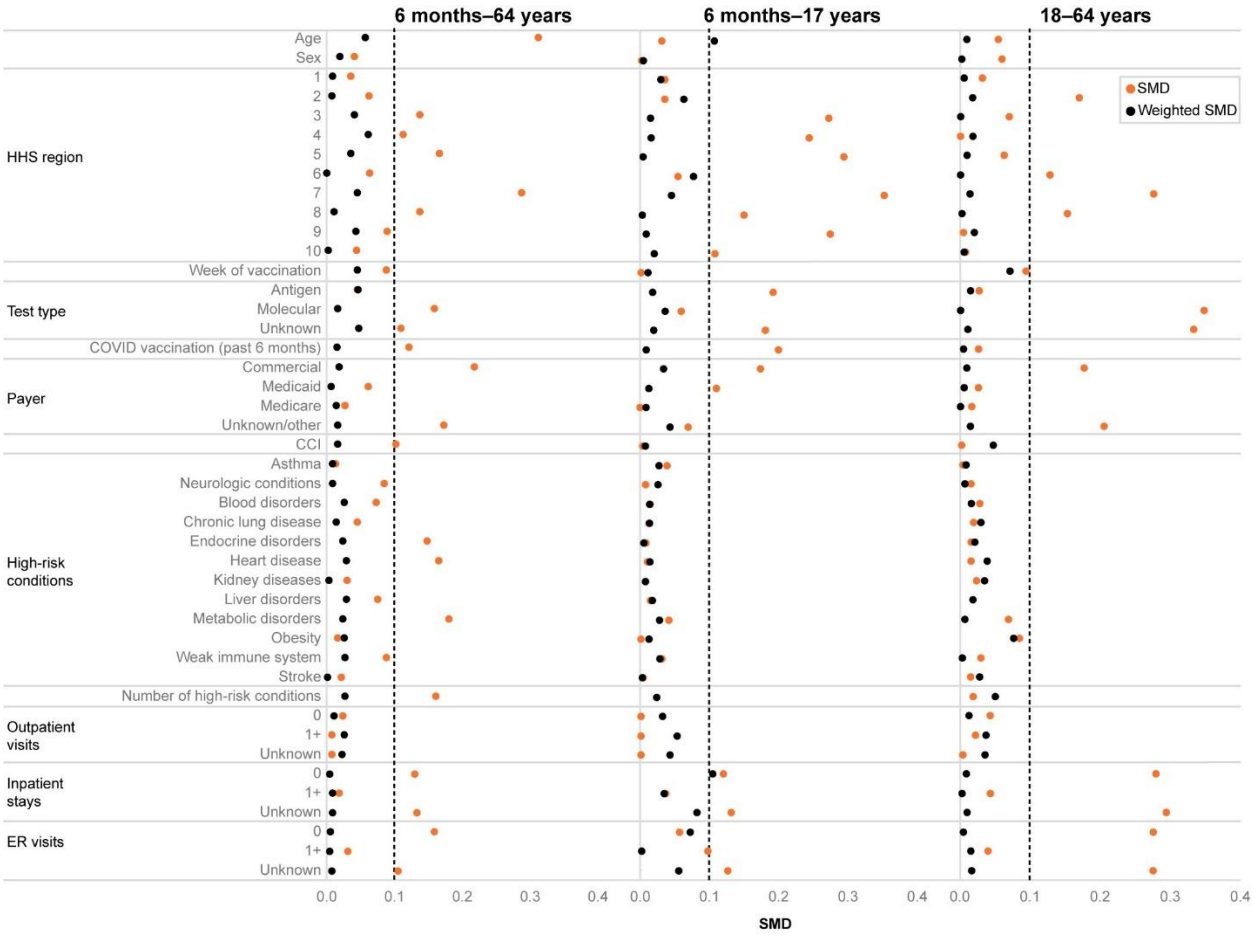
Dotted line indicates the threshold for imbalance between the vaccine groups: |SMD| >0.1.

HHS region 1 includes Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, Vermont, region 2 includes New Jersey, New York, Puerto Rico, the Virgin Islands, region 3 includes Delaware, District of Columbia, Maryland, Pennsylvania Virginia, West Virginia, region 4 includes Alabama, Florida, Georgia, Kentucky, Mississippi, North Carolina, South Carolina, Tennessee, region 5 includes Illinois, Indiana, Michigan, Minnesota, Ohio, Wisconsin, region 6 includes Arkansas, Louisiana, New Mexico, Oklahoma, Texas, region 7 includes Iowa,

Kansas, Missouri, Nebraska, region 8 includes Colorado, Montana, North Dakota, South Dakota, Utah, Wyoming, region 9 includes Arizona, California, Hawaii, Nevada, American Samoa, Commonwealth of the Northern Mariana Islands, Federated States of Micronesia, Guam, Marshall Islands, Republic of Palau and region 10 includes Alaska, Idaho, Oregon, Washington.

ER, emergency room; HHS, US. Department of Health and Human Services; QIVc, cell-based quadrivalent influenza vaccine; QIVe, egg-based quadrivalent influenza vaccine; SMD, standardized mean difference; US, United States.

Supplementary Figure 2. Covariate balance between vaccine groups (QIVc and QIVe) among test negative controls, before and after weighting, in outpatients of all ages, those aged 6 months–17 years, and those aged 18–64 years (2023–2024 influenza season in the US)



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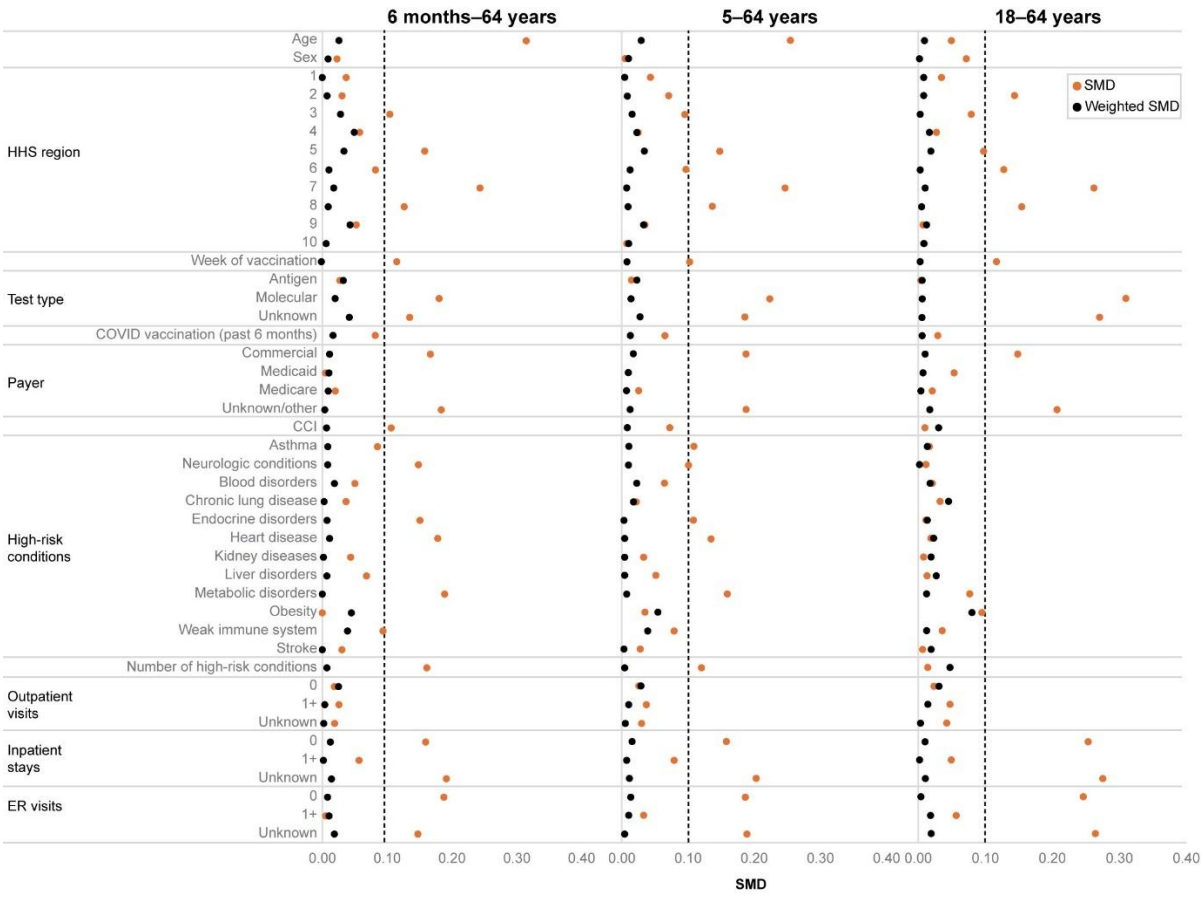
Supplementary Figure 3. Covariate balance between vaccine groups (QIVc and QIVe) among test negative controls, before and after weighting, in high-risk patients of all ages, aged 5–64 years, and aged 18–64 years (2023–2024 influenza season in the US)



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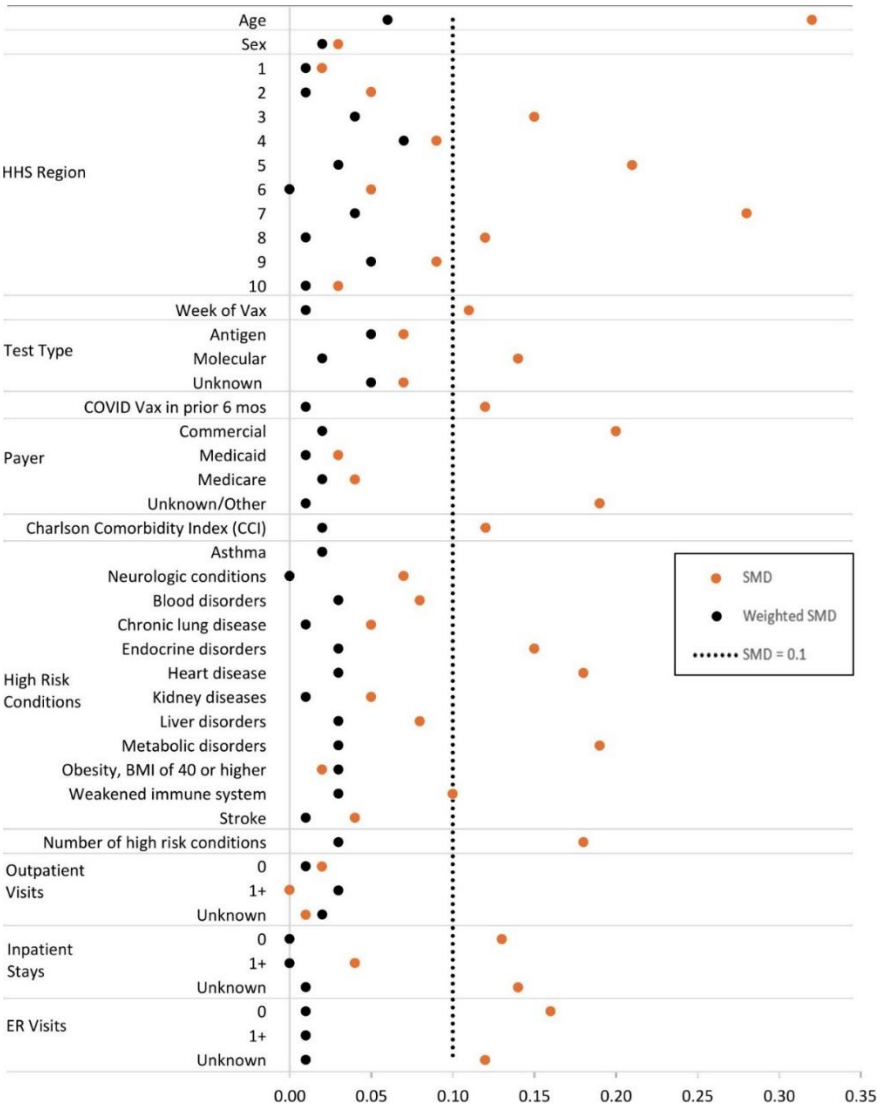
Supplementary Figure 4. Covariate balance between vaccine groups (QIVc and QIVe) among test negative controls, before and after weighting, in patients matched on test week (2023–2024 influenza season in the US)



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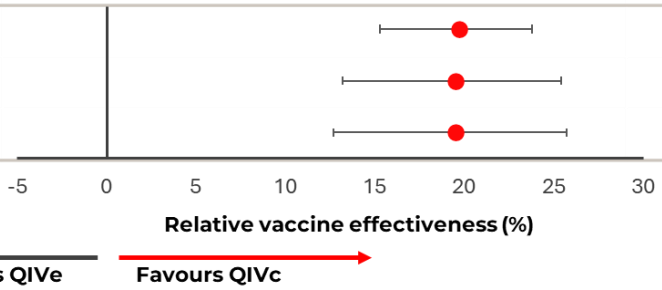
Supplementary Figure 5. rVE of QIVc vs. QIVe in prevention of test-confirmed influenza among outpatient subpopulations during the 2023–2024 influenza season in the US

Analysis	Age	Cases, n	Controls, n	Adjusted rVE (95% CI)
Outpatients				
All	6m – 64y	15,701	81,458	19.7% (15.3–23.8)
Pediatric	6m – 17y	10,868	45,313	19.5% (13.2–25.4)
Adult	18 – 64 yr	4,833	36,145	19.5% (12.7–25.7)

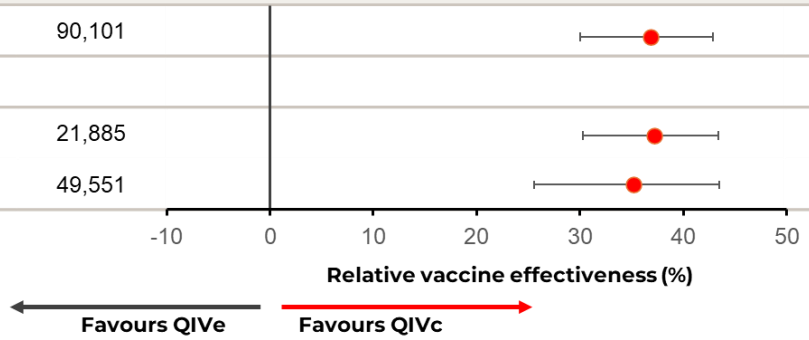


rVE was adjusted using a doubly robust approach combining inverse probability of treatment weighting and multivariable adjustment. rVE models were adjusted for age (as spline), sex, geographic region (HHS), influenza test date (as spline), and COVID-19 vaccination as well as other imbalanced covariates (**Supplementary Table 5**).

CI, confidence interval; HHS, US. Department of Health and Human Services; QIVc, cell-based quadrivalent influenza vaccine; QIVe, egg-based quadrivalent influenza vaccine; rVE, relative vaccine effectiveness; US, United States.

Supplementary Figure 6. rVE of QIVc vs. QIVe in the prevention of test-confirmed influenza B during the 2023–2024 influenza season in the US, main and confirmatory analyses

Analysis	Age	Cases, n	Controls, n	Adjusted rVE (95% CI)
Influenza B	6m – 64y	4,337	90,101	36.8% (30.0–42.9)
Post-hoc exploration				
Matched on test week	6m – 64y	4,337	21,885	37.2% (30.3–43.4)
Pediatric	6m – 17y	3,342	49,551	35.2% (25.6–43.5)



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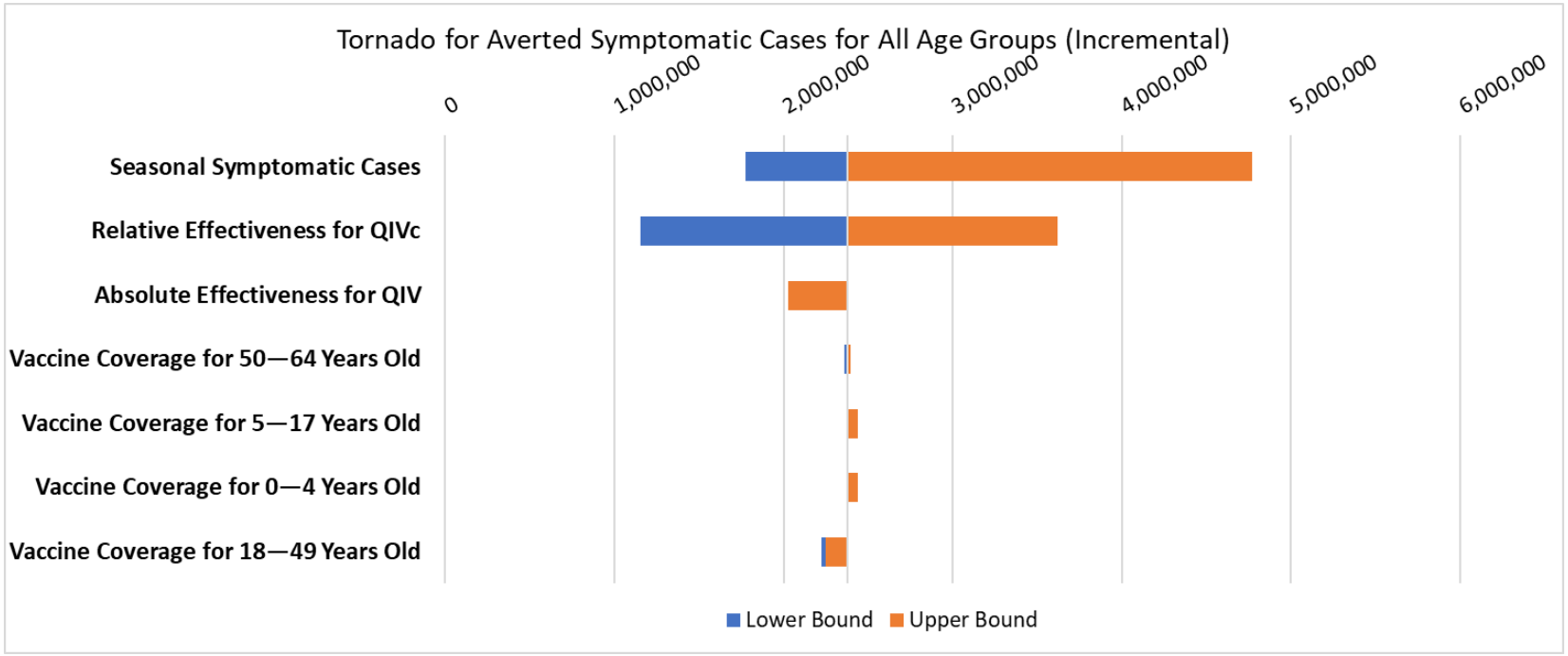
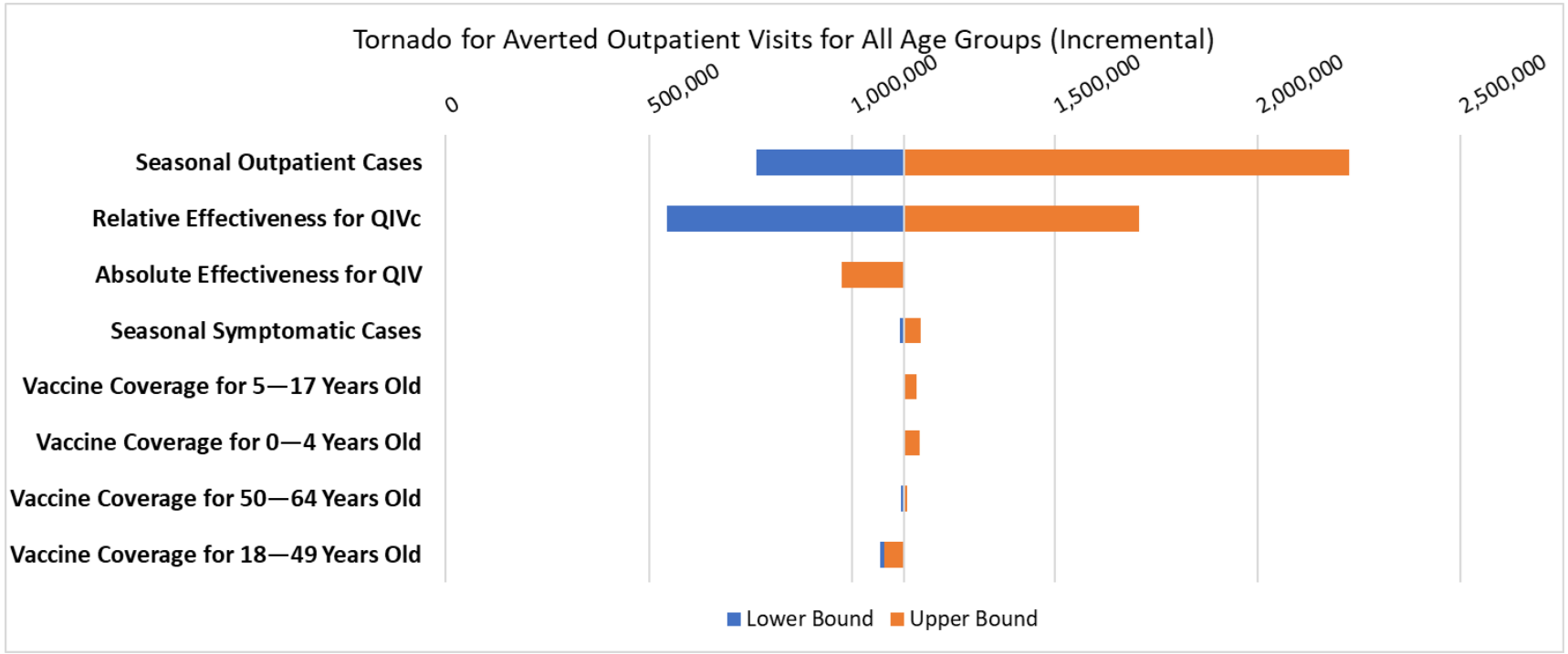
Supplementary Figure 7. Deterministic sensitivity analysis of uncertainty around the base-case results of the analysis of symptomatic cases averted

The deterministic sensitivity analysis evaluated the impact that individual model parameters had on the results by evaluating the change in the number of outcomes prevented from base case analysis when using the upper and lower limits of the 95% CIs of the estimates instead of the point estimate.

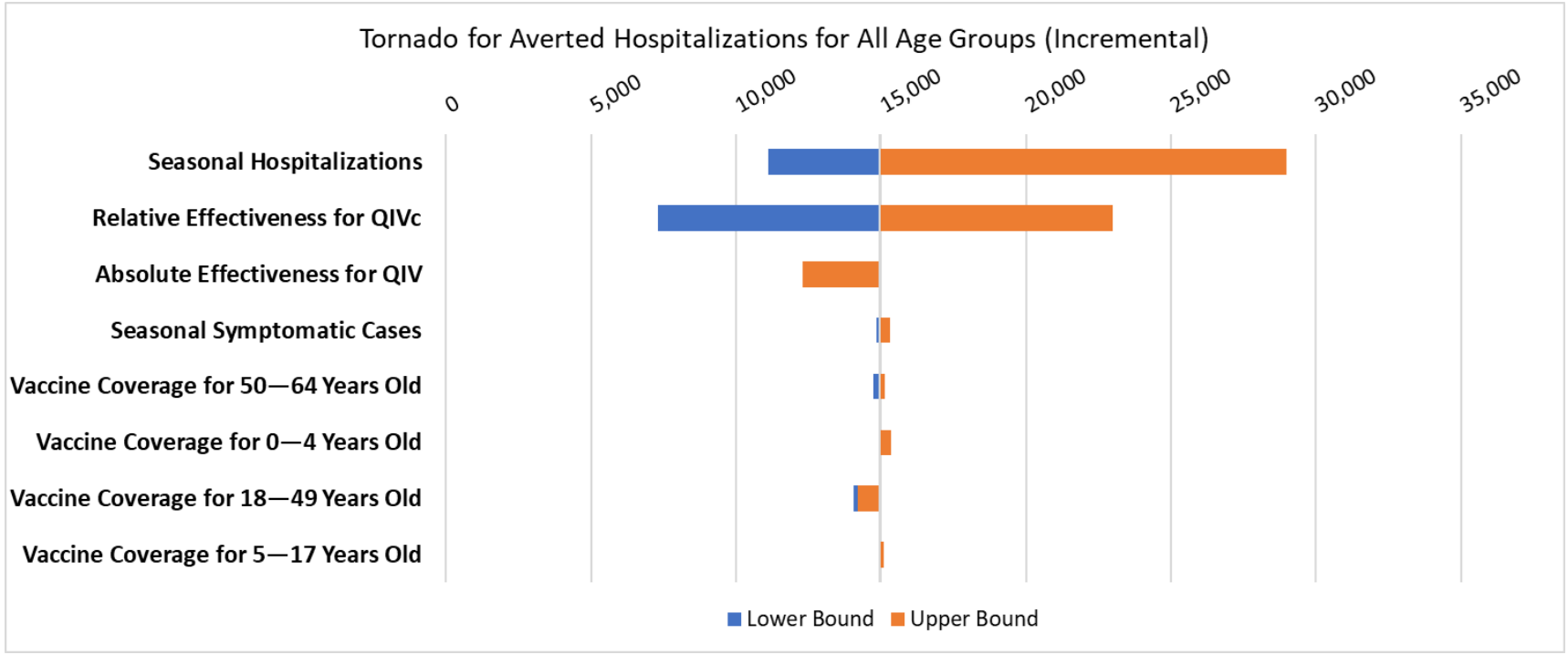
(A) Symptomatic cases



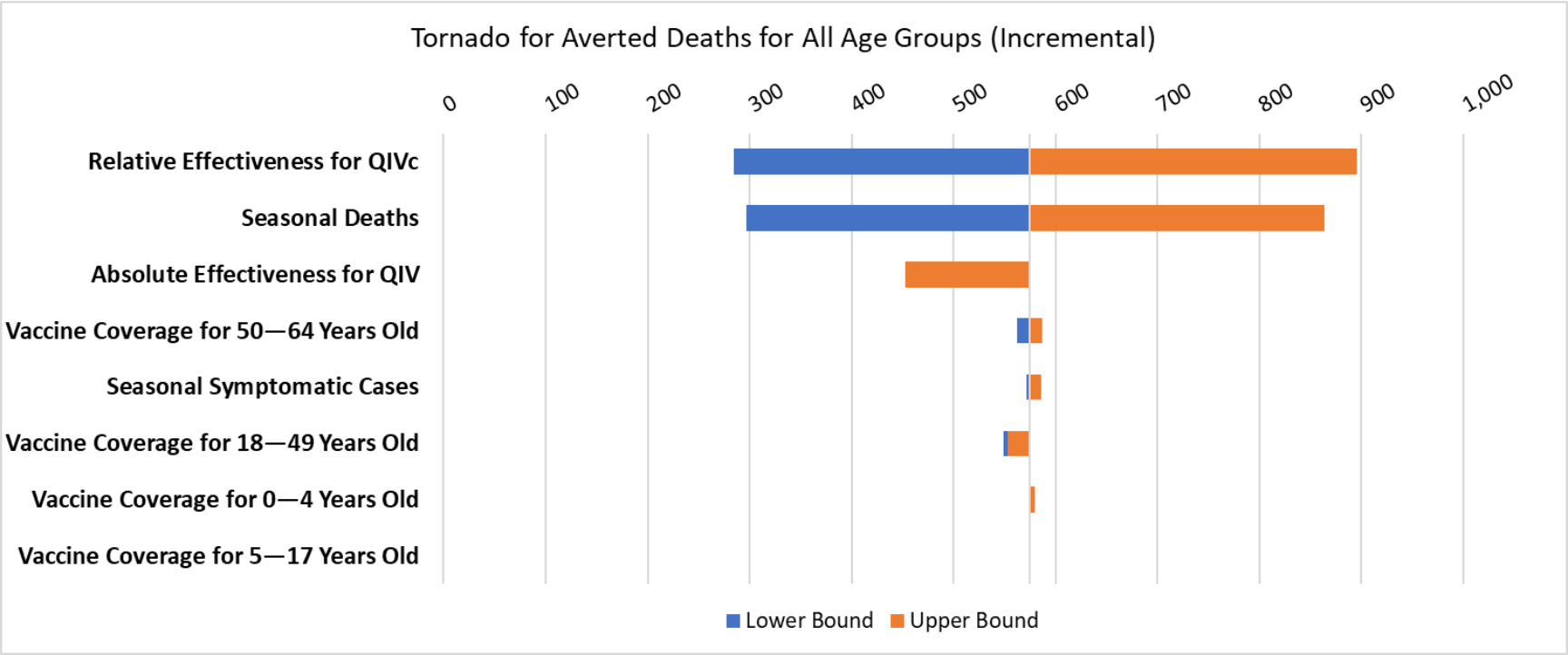
(B) Outpatient visits



(C) Hospitalizations



(D) Deaths

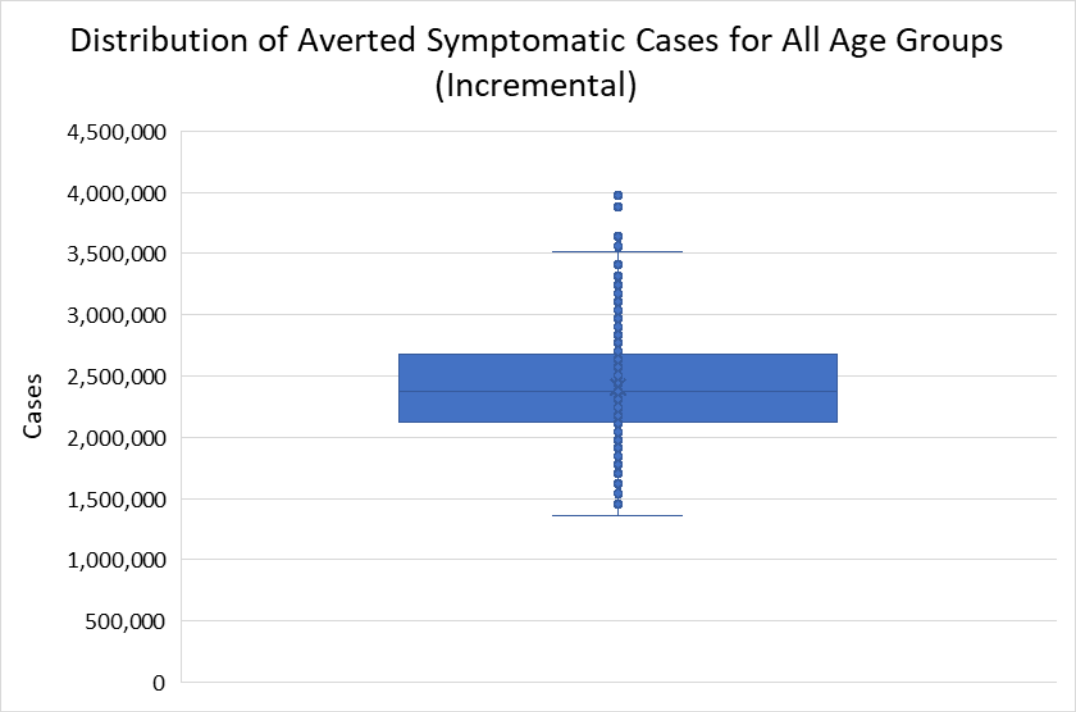


CI, confidence interval; QIVc, cell-based quadrivalent influenza vaccine; QIV, egg-based quadrivalent influenza vaccine.

Supplementary Figure 8. Probabilistic sensitivity analysis

The PSA evaluated the distribution of expected results after repeatedly resampling the input parameters over an assumed distribution. The center blue line represents the incremental mean, and the lower and upper bounds of the box represent the first and third quartiles of the incremental results, respectively. Dots represent individual observations, and whiskers represent 1.5 times the IQR.

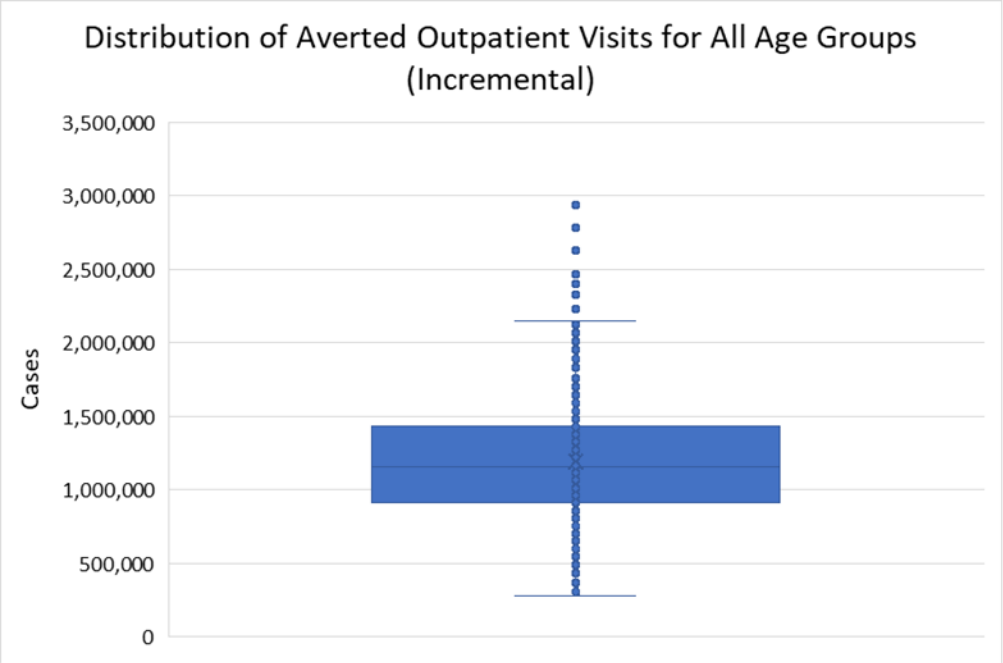
(A) Symptomatic cases



QIV Cases Averted By Outcome (For Incremental) - All Age Groups

Scenario	Mean	First Quartile	Third Quartile
QIVc	9,621,491	8,931,133	10,268,412
QIV	7,212,351	6,700,102	7,736,112
Incremental	2,409,140	2,124,769	2,680,538

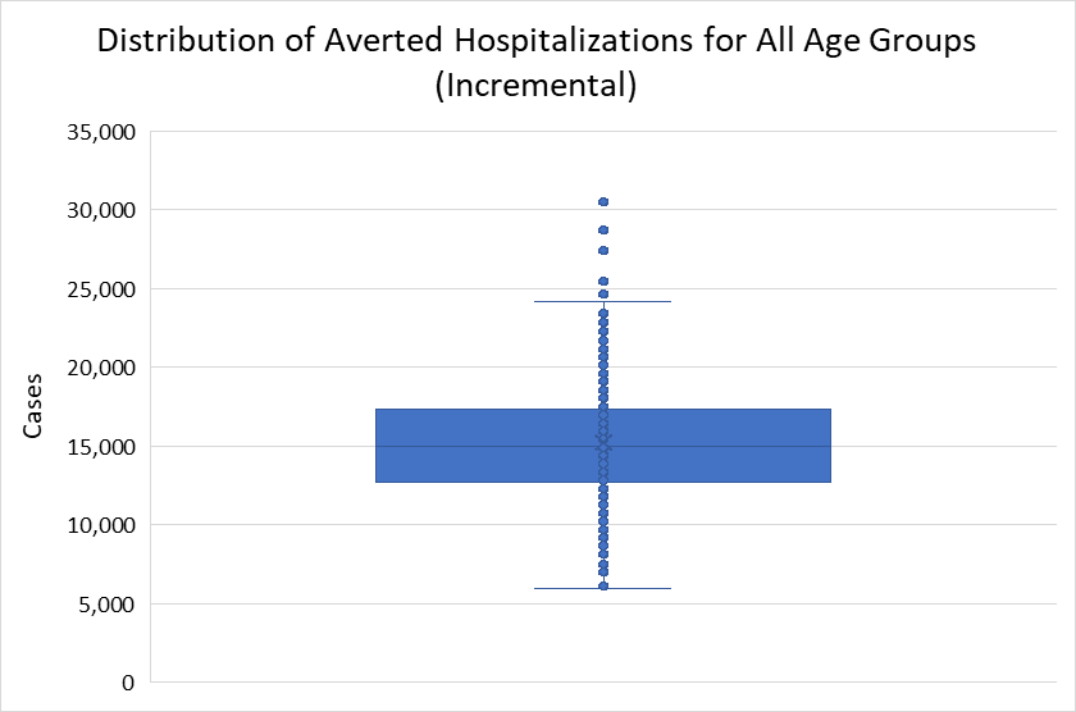
(B) Outpatient visits



QIV Cases Averted By Outcome (For Incremental) - All Age Groups

Scenario	Mean	First Quartile	Third Quartile
QIVc	4,895,931	3,763,973	5,869,804
QIV	3,705,838	2,810,432	4,482,763
Incremental	1,190,093	916,908	1,435,151

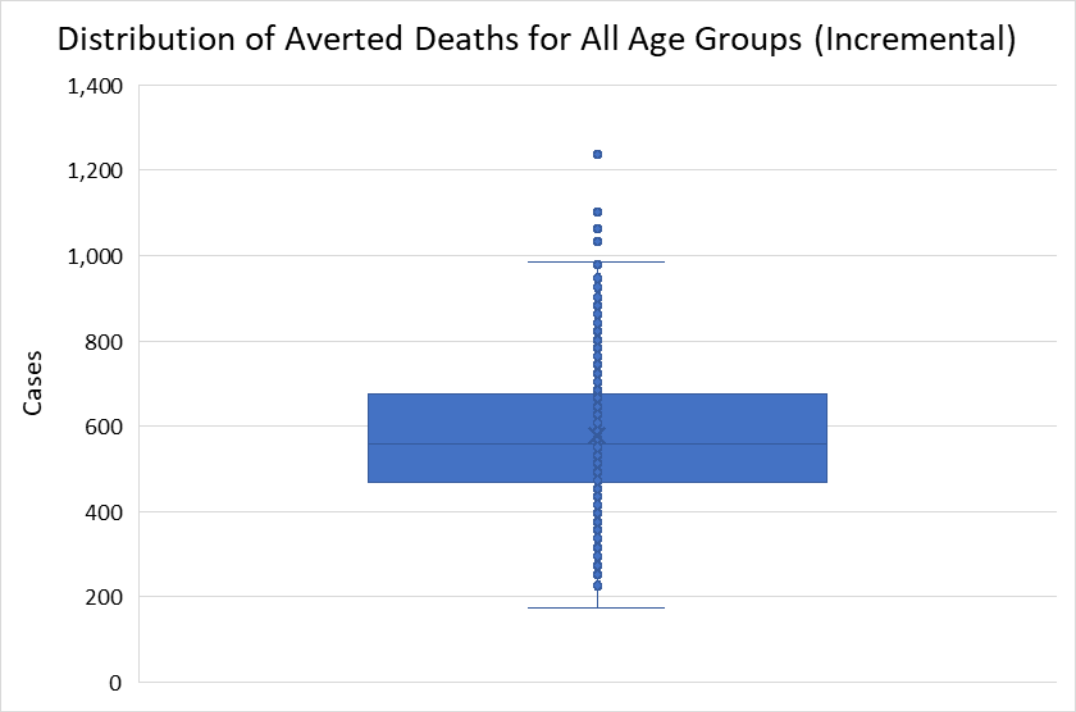
(C) Hospitalizations



QIV Cases Averted By Outcome (For Incremental) - All Age Groups

Scenario	Mean	First Quartile	Third Quartile
QIVc	49,847	44,337	55,072
QIV	34,655	30,926	38,301
Incremental	15,192	12,659	17,336

(D) Deaths



QIV Cases Averted By Outcome (For Incremental) - All Age Groups

Scenario	Mean	First Quartile	Third Quartile
QIVc	1,455	1,280	1,622
QIV	877	780	971
Incremental	578	469	675

IQR, interquartile range; PSA, probabilistic sensitivity analysis; QIVc, cell-based quadrivalent influenza vaccine; QIV, egg-based quadrivalent influenza vaccine.

Supplementary Table 1. Acute respiratory of febrile illness codes.

Acute Respiratory or Febrile Illness	**ICD-10-CM Code**
Sepsis, unspecified organism	A41.9
Viral infection of unspecified site	B34
Adenovirus infection, unspecified	B34.0
Enterovirus infection, unspecified	B34.1
Coronavirus infection, unspecified	B34.2
Parvovirus infection, unspecified	B34.3
Papovavirus infection, unspecified	B34.4
Other viral infection, unspecified	B34.8
Viral infection, unspecified	B34.9
Respiratory syncytial virus as the cause of diseases classified elsewhere	B97.4
Other viral agents as the cause of diseases classified elsewhere	B97.8
Human metapneumovirus as the cause of diseases classified elsewhere	B97.81
Other viral agents as the cause of diseases classified elsewhere	B97.89
Acute nasopharyngitis	J00
Acute sinusitis	J01
Acute maxillary sinusitis	J01.0
Acute maxillary sinusitis, unspecified	J01.00
Acute recurrent maxillary sinusitis	J01.01
Acute frontal sinusitis	J01.1
Acute frontal sinusitis, unspecified	J01.10
Acute recurrent frontal sinusitis	J01.11
Acute ethmoidal sinusitis	J01.2
Acute ethmoidal sinusitis, unspecified	J01.20
Acute recurrent ethmoidal sinusitis	J01.21
Acute sphenoidal sinusitis	J01.3
Acute sphenoidal sinusitis, unspecified	J01.30
Acute recurrent sphenoidal sinusitis	J01.31
Acute pansinusitis	J01.4

Acute pansinusitis, unspecified	J01.40
Acute recurrent pansinusitis	J01.41
Other acute sinusitis	J01.8
Other acute sinusitis	J01.80
Other acute recurrent sinusitis	J01.81
Other acute sinusitis	J01.9
Acute sinusitis, unspecified	J01.90
Acute recurrent sinusitis, unspecified	J01.91
Acute pharyngitis	J02
Streptococcal pharyngitis	J02.0
Acute pharyngitis due to other specified organisms	J02.8
Acute pharyngitis, unspecified	J02.9
Acute tonsillitis	J03
Streptococcal tonsillitis	J03.0
Acute streptococcal tonsillitis, unspecified	J03.00
Acute recurrent streptococcal tonsillitis	J03.01
Acute tonsillitis due to other specified organisms	J03.8
Acute tonsillitis due to other specified organisms	J03.80
Acute recurrent tonsillitis due to other specified organisms	J03.81
Acute tonsillitis, unspecified	J03.9
Acute tonsillitis, unspecified	J03.90
Acute recurrent tonsillitis, unspecified	J03.91
Acute laryngitis and tracheitis	J04
Acute laryngitis	J04.0
Acute tracheitis	J04.1
Acute tracheitis without obstruction	J04.10
Acute tracheitis with obstruction	J04.11
Acute laryngotracheitis	J04.2
Supraglottitis, unspecified	J04.3
Supraglottitis, unspecified, without obstruction	J04.30

Supraglottitis, unspecified, with obstruction	J04.31
Acute obstructive laryngitis [croup] and epiglottitis	J05
Acute obstructive laryngitis [croup]	J05.0
Acute epiglottitis	J05.1
Acute epiglottitis without obstruction	J05.10
Acute epiglottitis with obstruction	J05.11
Acute upper respiratory infections of multiple and unspecified sites	J06
Acute laryngopharyngitis	J06.0
Other acute upper respiratory infections of multiple sites	J06.8
Acute upper respiratory infection, unspecified	J06.9
Influenza due to certain identified influenza viruses	J09
Influenza due to identified novel influenza A virus	J09.X
Influenza due to identified novel influenza A virus with pneumonia	J09.X1
Influenza due to identified novel influenza A virus with other respiratory manifestations	J09.X2
Influenza due to identified novel influenza A virus with gastrointestinal manifestations	J09.X3
Influenza due to identified novel influenza A virus with other manifestations	J09.X9
Influenza due to other identified influenza virus	J10
Influenza due to other identified influenza virus with pneumonia	J10.0
Influenza due to other identified influenza virus with unspecified type of pneumonia	J10.00
Influenza due to other identified influenza virus with the same other identified influenza virus pneumonia	J10.01
Influenza due to other identified influenza virus with other specified pneumonia	J10.08
Influenza due to other identified influenza virus with other respiratory manifestations	J10.1

Influenza due to other identified influenza virus with gastrointestinal manifestations	J10.2
Influenza due to other identified influenza virus with other manifestations	J10.8
Influenza due to other identified influenza virus with encephalopathy	J10.81
Influenza due to other identified influenza virus with myocarditis	J10.82
Influenza due to other identified influenza virus with otitis media	J10.83
Influenza due to other identified influenza virus with other manifestations	J10.89
Influenza due to unidentified influenza virus	J11
Influenza due to unidentified influenza virus with pneumonia	J11.0
Influenza due to unidentified influenza virus with unspecified type of pneumonia	J11.00
Influenza due to unidentified influenza virus with specified pneumonia	J11.08
Influenza due to unidentified influenza virus with other respiratory manifestations	J11.1
Influenza due to unidentified influenza virus with gastrointestinal manifestations	J11.2
Influenza due to unidentified influenza virus with other manifestations	J11.8
Influenza due to unidentified influenza virus with encephalopathy	J11.81
Influenza due to unidentified influenza virus with myocarditis	J11.82
Influenza due to unidentified influenza with otitis media	J11.83
Influenza due to unidentified influenza virus with other manifestations	J11.89
Viral pneumonia, not elsewhere classified	J12
Adenoviral pneumonia	J12.0
Respiratory syncytial virus pneumonia	J12.1
Parainfluenza virus pneumonia	J12.2
Human metapneumovirus pneumonia	J12.3
Other viral pneumonia	J12.8
Pneumonia due to SARS-associated coronavirus	J12.81

Pneumonia due to coronavirus disease 2019*	J12.82
Other viral pneumonia	J12.89
Viral pneumonia, unspecified	J12.9
Pneumonia due to Streptococcus pneumoniae	J13
Pneumonia due to Hemophilus influenzae	J14
Bacterial pneumonia, not elsewhere classified	J15
Pneumonia due to Klebsiella pneumoniae	J15.0
Pneumonia due to Pseudomonas	J15.1
Pneumonia due to staphylococcus	J15.2
Pneumonia due to staphylococcus, unspecified	J15.20
Pneumonia due to staphylococcus aureus	J15.21
Pneumonia due to Methicillin susceptible Staphylococcus aureus	J15.211
Pneumonia due to Methicillin resistant Staphylococcus aureus	J15.212
Pneumonia due to other staphylococcus	J15.29
Pneumonia due to streptococcus, group B	J15.3
Pneumonia due to other streptococci	J15.4
Pneumonia due to Escherichia coli	J15.5
Pneumonia due to other aerobic Gram-negative bacteria	J15.6
Pneumonia due to Mycoplasma pneumoniae	J15.7
Pneumonia due to other specified bacteria	J15.8
Unspecified bacterial pneumonia	J15.9
Pneumonia due to other infectious organisms, not elsewhere classified	J16
Chlamydial pneumonia	J16.0
Pneumonia due to other specified infectious organisms	J16.8
Pneumonia in diseases classified elsewhere	J17
Pneumonia, unspecified organism	J18
Bronchopneumonia, unspecified organism	J18.0
Lobar pneumonia, unspecified organism	J18.1
Hypostatic pneumonia, unspecified organism	J18.2
Other pneumonia, unspecified organism	J18.8

Pneumonia, unspecified organism	J18.9
Acute bronchitis	J20
Acute bronchitis due to Mycoplasma pneumoniae	J20.0
Acute bronchitis due to Hemophilus influenzae	J20.1
Acute bronchitis due to streptococcus	J20.2
Acute bronchitis due to coxsackievirus	J20.3
Acute bronchitis due to parainfluenza virus	J20.4
Acute bronchitis due to respiratory syncytial virus	J20.5
Acute bronchitis due to rhinovirus	J20.6
Acute bronchitis due to echovirus	J20.7
Acute bronchitis due to other specified organisms	J20.8
Acute bronchitis, unspecified	J20.9
Acute bronchiolitis	J21
Acute bronchiolitis due to respiratory syncytial virus	J21.0
Acute bronchiolitis due to human metapneumovirus	J21.1
Acute bronchiolitis due to other specified organisms	J21.8
Acute bronchiolitis, unspecified	J21.9
Unspecified acute lower respiratory infection	J22
Chronic sinusitis	J32
Chronic maxillary sinusitis	J32.0
Chronic frontal sinusitis	J32.1
Chronic ethmoidal sinusitis	J32.2
Chronic sphenoidal sinusitis	J32.3
Chronic pansinusitis	J32.4
Other chronic sinusitis	J32.8
Chronic sinusitis, unspecified	J32.9
Other specified diseases of upper respiratory tract	J39.8
Disease of upper respiratory tract, specified	J39.9
Bronchitis, not specified as acute or chronic	J40
Simple and mucopurulent chronic bronchitis	J41

Simple chronic bronchitis	J41.0
Mucopurulent chronic bronchitis	J41.1
Mixed simple and mucopurulent chronic bronchitis	J41.8
Unspecified chronic bronchitis	J42
Emphysema	J43
Unilateral pulmonary emphysema [MacLeod's syndrome]	J43.0
Panlobular emphysema	J43.1
Centrilobular emphysema	J43.2
Other emphysema	J43.8
Emphysema, unspecified	J43.9
COPD with acute lower respiratory infection	J44.0
COPD with acute exacerbation	J44.1
Mild intermittent asthma with (acute) exacerbation	J45.21
Mild intermittent asthma with status asthmaticus	J45.22
Mild persistent asthma with (acute) exacerbation	J45.31
Mild persistent asthma with status asthmaticus	J45.32
Moderate persistent asthma with (acute) exacerbation	J45.41
Moderate persistent asthma with status asthmaticus	J45.42
Severe persistent asthma with (acute) exacerbation	J45.51
Severe persistent asthma with status asthmaticus	J45.52
Unspecified asthma with (acute) exacerbation	J45.901
Unspecified asthma with status asthmaticus	J45.902
Bronchiectasis	J47
Bronchiectasis with acute lower respiratory infection	J47.0
Bronchiectasis with (acute) exacerbation	J47.1
Bronchiectasis, uncomplicated	J47.9
Acute respiratory distress syndrome	J80
Pulmonary edema	J81
Acute pulmonary edema	J81.0
Chronic pulmonary edema	J81.1

Abscess of lung and mediastinum	J85
Gangrene and necrosis of lung	J85.0
Abscess of lung with pneumonia	J85.1
Abscess of lung without pneumonia	J85.2
Abscess of mediastinum	J85.3
Pyothorax	J86
Pyothorax with fistula	J86.0
Pyothorax without fistula	J86.9
Pleural effusion, not elsewhere classified	J90
Acute respiratory failure	J96.0
Acute respiratory failure, unspecified whether with hypoxia or hypercapnia	J96.00
Acute respiratory failure with hypoxia	J96.01
Acute respiratory failure with hypercapnia	J96.02
Acute and chronic respiratory failure	J96.2
Acute and chronic respiratory failure, unspecified whether with hypoxia or hypercapnia	J96.20
Acute and chronic respiratory failure with hypoxia	J96.21
Acute and chronic respiratory failure with hypercapnia	J96.22
Respiratory failure, unspecified, unspecified	J96.9
Respiratory failure, unspecified, unspecified whether with hypoxia or hypercapnia	J96.90
Respiratory failure, unspecified with hypoxia	J96.91
Respiratory failure, unspecified with hypercapnia	J96.92
Other diseases of bronchus, not elsewhere classified	J98.09
Pulmonary collapse	J98.1
Atelectasis	J98.11
Other pulmonary collapse	J98.19
Other disorders of lung	J98.4
Other specified respiratory disorders	J98.8

Respiratory disorder, unspecified	J98.9
Shock during or following labor and delivery	O75.1
Pyrexia during labor, not elsewhere classified	O75.2
Pyrexia of unknown origin following delivery	O86.4
Other viral diseases complicating pregnancy/childbirth	O98.5
Other viral diseases complicating pregnancy	O98.51
Other viral diseases complicating pregnancy, first trimester	O98.511
Other viral diseases complicating pregnancy, second trimester	O98.512
Other viral diseases complicating pregnancy, third trimester	O98.513
Other viral diseases complicating pregnancy, unspecified trimester	O98.519
Other viral diseases complicating childbirth	O98.52
Other viral diseases complicating the puerperium	O98.53
Other maternal infectious and parasitic diseases complicating pregnancy	O98.81
Other maternal infectious and parasitic diseases complicating pregnancy, first trimester	O98.811
Other maternal infectious and parasitic diseases complicating pregnancy, second trimester	O98.812
Other maternal infectious and parasitic diseases complicating pregnancy, third trimester	O98.813
Other maternal infectious and parasitic diseases complicating pregnancy, unspecified trimester	O98.819
Diseases of the respiratory system complicating pregnancy	O99.51
Diseases of the respiratory system complicating pregnancy, first trimester	O99.511
Diseases of the respiratory system complicating pregnancy, second trimester	O99.512
Diseases of the respiratory system complicating pregnancy, third trimester	O99.513
Diseases of the respiratory system complicating pregnancy, unspecified trimester	O99.519

Hemoptysis	R04.2
Cough	R05
Acute cough	R05.1
Subacute cough	R05.2
Chronic cough	R05.3
Cough syncope	R05.4
Other specified cough	R05.8
Cough, unspecified	R05.9
Dyspnea	R06.0
Dyspnea, unspecified	R06.00
Orthopnea	R06.01
Shortness of breath	R06.02
Acute respiratory distress	R06.03
Other forms of dyspnea	R06.09
Stridor	R06.1
Wheezing	R06.2
Other abnormalities of breathing	R06.8
Apnea, not elsewhere classified	R06.81
Tachypnea, not elsewhere classified	R06.82
Other abnormalities of breathing/ Other symptoms involving head & neck	R06.89
Chest pain on breathing	R07.1
Asphyxia and hypoxemia	R09.0
Asphyxia	R09.01
Hypoxemia	R09.02
Pleurisy	R09.1
Respiratory arrest	R09.2
Abnormal sputum	R09.3
Other specified symptoms and signs involving the circulatory and respiratory systems	R09.8

Nasal congestion	R09.81
Postnasal drip	R09.82
Other specified symptoms and signs involving the circulatory and respiratory systems	R09.89
Fever of other and unknown origin*	R50
Drug induced fever	R50.2
Other specified fever	R50.8
Fever presenting with conditions classified elsewhere	R50.81
Postprocedural fever	R50.82
Postvaccination fever	R50.83
Febrile nonhemolytic transfusion reaction	R50.84
Fever, unspecified	R50.9
Shock, unspecified	R57.9
Severe sepsis with septic shock	R65.21
Chills (without fever)	R68.83
COVID-19, virus identified	U07.1
COVID-19, virus not identified	U07.2

COPD, Chronic obstructive pulmonary disease.

Supplementary Table 2. CVX, CPT and NDC codes for 2023–2024 influenza vaccines

Vaccine Type	CVX Codes	CPT/HCPCS Codes	NDC Codes
QIVe	150, 158	90685, 90686, 90687, 90688	**2021–2022:** 19515-0818-41, 19515-0818-52, 33332-0221-20, 33332-0221-21, 33332-0321-01, 33332-0321-02, 33332-0421-10, 33332-0421-11, 49281-0521-00, 49281-0521-25, 49281-0421-88, 49281-0421-50, 49281-0421-58, 49281-0421-10, 49281-0635-78, 49281-0635-15, 58160-0887-41, 58160-0887-52 **2022–2023:** 19515-0808-41, 19515-0808-52, 33332-0322-03, 33332-0322-04, 33332-0422-10, 33332-0422-11, 49281-0422-10, 49281-0422-50, 49281-0422-58, 49281-0422-88, 49281-0637-15, 49281-0637-78, 58160-0890-41, 58160-0890-52 **2023–2024:** 19515-0814-41, 19515-0814-52, 33332-0323-03, 33332-0323-04, 33332-0423-10, 33332-0423-11, 49281-0423-50, 49281-0423-88, 49281-0639-15, 49281-0639-78, 58160-0909-41, 58160-0909-52
QIVc	171, 186	90674, 90756	**2021–2022:** 70461-0321-03, 70461-0321-04, 70461-0421-10, 70461-0421-11 **2022–2023:** 70461-0322-03, 70461-0322-04, 70461-0422-10, 70461-0422-11 **2023–2024:** 70461-0323-03, 70461-0323-04, 70461-0423-10, 70461-0423-11
Adjuvanted	205	90689, 90694	**2021–2022:** 70461-0121-03, 70461-0121-04 **2022–2023:** 70461-0122-03, 70461-0122-04 **2023–2024:** 70461-0123-03, 70461-0123-04

High dose	135, 197	90662	**2021–2022:** 49281-0121-65, 49281-0121-88 **2022–2023:** 49281-0122-88, 49281-0122-65 **2023–2024:** 49281-012388, 49281-0123-65
LAIV	149	90672	**2021–2022:** 66019-0308-01, 66019-0308-10 **2022–2023:** 66019-0309-10, 66019-0309-01 **2023–2024:** 66019-0310-10, 66019-0310-01
Recombinant	185	90682	**2021–2022:** 49281-0721-88, 49281-0721-10 **2022–2023:** 49281-0722-88, 49281-0722-10 **2023–2024:** 49281-0723-88, 49281-0723-10
Unspecified		Q2039 G0008	

* Three different coding systems are used to identify vaccines: CPT, CVX, and NDC. CPT codes identify medical services and procedures (including immunizations) and are managed by the AMA. CVX codes indicate the product used in a vaccination and are created when a vaccine is approved by the FDA. CVX codes are managed by the CDC. NDC codes are universal product identifiers for drugs and are managed by the FDA. CPT and CVX codes are not season-specific, whereas NDC codes are season-specific to reflect distinct formulations. Any of the code types may appear in EHR data. CPT and NDC codes are used for billing purposes and appear in claim records.

AMA, American Medical Association; CDC, Centers for Disease Control and Prevention; CPT, current procedural terminology; CVX, vaccine administered code set; FDA, Food and Drug Administration; HCPCS, Healthcare Common Procedure Coding System; LAIV, live attenuated influenza vaccine; NDC, National Drug Code; QIVc, cell-based quadrivalent influenza vaccine; QIVe, egg-based quadrivalent influenza vaccine.

Supplementary Table 3. Influenza test codes

Code type	Code	Long Name	Test Type
CPT	87275	Infectious agent antigen detection by immunofluorescent technique; influenza B virus	Ag
CPT	87276	Infectious agent antigen detection by immunofluorescent technique; influenza A virus	Ag
CPT	87400	Infectious agent antigen detection by immunoassay technique, (e.g., enzyme immunoassay [EIA], enzyme-linked immunosorbent assay [ELISA], fluorescence immunoassay [FIA], immunochemiluminometric assay [IMCA]) qualitative or semiquantitative; Influenza, A or B, each	Ag
CPT	87501	Infectious agent detection by nucleic acid (DNA or RNA); influenza virus, includes reverse transcription, when performed, and amplified probe technique, each type or subtype	M
CPT	87502	Infectious agent detection by nucleic acid (DNA or RNA); influenza virus, for multiple types or sub- types, includes multiplex reverse transcription, when performed, and multiplex amplified probe technique, first 2 types or sub-types	M
CPT	87503	Infectious agent detection by nucleic acid (DNA or RNA); influenza virus, for multiple types or sub- types, includes multiplex reverse transcription, when performed, and multiplex amplified probe technique, each additional influenza virus type or sub-type beyond 2 (List separately in addition to code for primary procedure)	M

Code type	Code	Long Name	Test Type
CPT	87804	Infectious agent antigen detection by immunoassay with direct optical observation; Influenza	Ag
LOINC	22825-4	Influenza virus A Ag [Presence] in Specimen by Immune diffusion (ID)	Ag
LOINC	24015-0	Influenza virus A+B Ag [Presence] in Specimen	Ag
LOINC	31858-4	Influenza virus A Ag [Presence] in Throat	Ag
LOINC	31859-2	Influenza virus A Ag [Presence] in Specimen	Ag
LOINC	31860-0	Influenza virus A+B Ag [Presence] in Throat	Ag
LOINC	31861-8	Influenza virus A+B+C Ag [Presence] in Throat	Ag
LOINC	31862-6	Influenza virus A+B+C Ag [Presence] in Specimen	Ag
LOINC	31863-4	Influenza virus B Ag [Presence] in Throat	Ag
LOINC	31864-2	Influenza virus B Ag [Presence] in Specimen	Ag
LOINC	33535-6	Influenza virus A+B Ag [Presence] in Nasopharynx	Ag
LOINC	34487-9	Influenza virus A RNA [Presence] in Specimen by NAA with probe detection	M
LOINC	38381-0	Influenza virus A cDNA [Presence] in Specimen by NAA with probe detection	M
LOINC	40981-3	Deprecated Influenza virus A RNA [Presence] in Unspecified specimen by Probe & target amplification method	M
LOINC	40982-1	Influenza virus B RNA [Presence] in Specimen by NAA with probe detection	M
LOINC	43874-7	Influenza virus A Ag [Presence] in Nasopharynx	Ag
LOINC	43895-2	Influenza virus B Ag [Presence] in Nasopharynx	Ag
LOINC	44558-5	Influenza virus A Ag [Presence] in Nasopharynx by Immunofluorescence	Ag
LOINC	44559-3	Influenza virus A Ag [Presence] in Bronchial specimen by Immunofluorescence	Ag

Code type	Code	Long Name	Test Type
LOINC	44560-1	Influenza virus A Ag [Presence] in Nose by Immunofluorescence	Ag
LOINC	44561-9	Influenza virus A Ag [Presence] in Trachea by Immunofluorescence	Ag
LOINC	44562-7	Influenza virus A Ag [Presence] in Bronchial specimen	Ag
LOINC	44563-5	Influenza virus A Ag [Presence] in Nose	Ag
LOINC	44564-3	Influenza virus A Ag [Presence] in Nose by Immunoassay	Ag
LOINC	44566-8	Influenza virus A+B Ag [Presence] in Bronchial specimen	Ag
LOINC	44567-6	Influenza virus A+B Ag [Presence] in Nose	Ag
LOINC	44571-8	Influenza virus B Ag [Presence] in Nasopharynx by Immunofluorescence	Ag
LOINC	44572-6	Influenza virus B Ag [Presence] in Bronchial specimen by Immunofluorescence	Ag
LOINC	44573-4	Influenza virus B Ag [Presence] in Nose by Immunofluorescence	Ag
LOINC	44574-2	Influenza virus B Ag [Presence] in Trachea by Immunofluorescence	Ag
LOINC	44575-9	Influenza virus B Ag [Presence] in Nose by Immunoassay	Ag
LOINC	44576-7	Influenza virus B Ag [Presence] in Bronchial specimen	Ag
LOINC	44577-5	Influenza virus B Ag [Presence] in Nose	Ag
LOINC	46082-4	Influenza virus A Ag [Presence] in Nasopharynx by Immunoassay	Ag
LOINC	46083-2	Influenza virus B Ag [Presence] in Nasopharynx by Immunoassay	Ag
LOINC	48509-4	Influenza virus A and B RNA [Identifier] in Specimen by NAA with probe detection	M
LOINC	49520-0	Influenza virus A H1 RNA [Presence] in Isolate by NAA with probe detection	M

Code type	Code	Long Name	Test Type
LOINC	49521-8	Influenza virus A H1 RNA [Presence] in Specimen by NAA with probe detection	M
LOINC	49522-6	Influenza virus A H3 Ag [Presence] in Isolate by Immunofluorescence	Ag
LOINC	49523-4	Influenza virus A H3 RNA [Presence] in Isolate by NAA with probe detection	M
LOINC	49524-2	Influenza virus A H3 RNA [Presence] in Specimen by NAA with probe detection	M
LOINC	49529-1	Influenza virus A Ag [Presence] in Isolate by Immunofluorescence	Ag
LOINC	49531-7	Influenza virus A RNA [Presence] in Isolate by NAA with probe detection	M
LOINC	49534-1	Influenza virus B Ag [Presence] in Isolate by Immunofluorescence	Ag
LOINC	49535-8	Influenza virus B RNA [Presence] in Isolate by NAA with probe detection	M
LOINC	49537-4	Influenza virus A and B RNA [Identifier] in Isolate by NAA with probe detection	M
LOINC	50697-2	Influenza virus A Ag [Identifier] in Isolate	Ag
LOINC	50701-2	Influenza virus A H1 Ag [Presence] in Isolate by Immunofluorescence	Ag
LOINC	50707-9	Influenza virus A polymerase B1 cDNA [Presence] in Isolate by Sequencing	M
LOINC	53381-0	Influenza virus A Ab [Identifier] in Serum	Ab
LOINC	54240-7	Influenza virus Ag [Presence] in Specimen	Ag
LOINC	54241-5	Influenza virus B Ag [Presence] in Isolate	Ag
LOINC	54243-1	Influenza virus RNA [Identifier] in Specimen by Probe	M
LOINC	54244-9	Influenza virus identified in Specimen	M

Code type	Code	Long Name	Test Type
LOINC	55465-9	Influenza virus A H1 2009 pandemic RNA [Presence] in Specimen by NAA with probe detection	M
LOINC	5860-2	Influenza virus A Ag [Presence] in Throat by Immunoassay	Ag
LOINC	5861-0	Influenza virus A Ag [Presence] in Throat by Immunofluorescence	Ag
LOINC	5862-8	Influenza virus A Ag [Presence] in Specimen by Immunoassay	Ag
LOINC	5863-6	Influenza virus A Ag [Presence] in Specimen by Immunofluorescence	Ag
LOINC	5864-4	Influenza virus B Ag [Presence] in Throat by Immunoassay	Ag
LOINC	5865-1	Influenza virus B Ag [Presence] in Throat by Immunofluorescence	Ag
LOINC	5866-9	Influenza virus B Ag [Presence] in Specimen by Immunoassay	Ag
LOINC	5867-7	Influenza virus B Ag [Presence] in Specimen by Immunofluorescence	Ag
LOINC	60538-6	Influenza virus A H1+H3+B RNA [Presence] in Specimen by NAA with probe detection	M
LOINC	61102-0	Influenza virus A and B Ag [Identifier] in Specimen by Immunofluorescence	Ag
LOINC	62462-7	Influenza virus A+B RNA [Presence] in Specimen by NAA with probe detection	M
LOINC	6435-2	Influenza virus A+B Ag [Presence] in Throat by Immunoassay	Ag
LOINC	6436-0	Influenza virus A+B Ag [Presence] in Throat by Immunofluorescence	Ag
LOINC	6437-8	Influenza virus A+B Ag [Presence] in Specimen by Immunoassay	Ag

Code type	Code	Long Name	Test Type
LOINC	6438-6	Influenza virus A+B Ag [Presence] in Specimen by Immunofluorescence	Ag
LOINC	6439-4	Influenza virus A+B+C Ag [Presence] in Throat by Immunoassay	Ag
LOINC	6440-2	Influenza virus A+B+C Ag [Presence] in Throat by Immunofluorescence	Ag
LOINC	6441-0	Influenza virus A+B+C Ag [Presence] in Specimen by Immunoassay	Ag
LOINC	6442-8	Influenza virus A+B+C Ag [Presence] in Specimen by Immunofluorescence	Ag
LOINC	72356-9	Influenza virus A and B Ag [Identifier] in Specimen by Rapid immunoassay	Ag
LOINC	72365-0	Influenza virus A and B Ag [Identifier] in Nose by Immunofluorescence	Ag
LOINC	72366-8	Influenza virus A and B Ag [Identifier] in Nose by Rapid immunoassay	Ag
LOINC	72367-6	Influenza virus A+B Ag [Presence] in Nose by Rapid immunoassay	Ag
LOINC	74784-0	Influenza virus B lineage RNA [Identifier] in Specimen by NAA with probe detection	M
LOINC	74785-7	Influenza virus B Victoria lineage RNA [Presence] in Specimen by NAA with probe detection	M
LOINC	74786-5	Influenza virus B Yamagata lineage RNA [Presence] in Specimen by NAA with probe detection	M
LOINC	76077-7	Influenza virus A RNA [Presence] in Bronchoalveolar lavage by NAA with probe detection	M
LOINC	76078-5	Influenza virus A RNA [Presence] in Nasopharynx by NAA with probe detection	M

Code type	Code	Long Name	Test Type
LOINC	76079-3	Influenza virus B RNA [Presence] in Bronchoalveolar lavage by NAA with probe detection	M
LOINC	76080-1	Influenza virus B RNA [Presence] in Nasopharynx by NAA with probe detection	M
LOINC	77026-3	Influenza virus A H1 RNA [Presence] in Nasopharynx by NAA with probe detection	M
LOINC	77027-1	Influenza virus A H3 RNA [Presence] in Nasopharynx by NAA with probe detection	M
LOINC	77028-9	Influenza virus A H1 2009 pandemic RNA [Presence] in Nasopharynx by NAA with probe detection	M
LOINC	77383-8	Influenza virus A Ag [Presence] in Bronchoalveolar lavage by Immunofluorescence	Ag
LOINC	77384-6	Influenza virus B Ag [Presence] in Bronchoalveolar lavage by Immunofluorescence	Ag
LOINC	80382-5	Influenza virus A Ag [Presence] in Upper respiratory specimen by Rapid immunoassay	Ag
LOINC	80383-3	Influenza virus B Ag [Presence] in Upper respiratory specimen by Rapid immunoassay	Ag
LOINC	80588-7	Influenza virus A M gene [Presence] in Nasopharynx by NAA with probe detection	M
LOINC	80589-5	Influenza virus A H1 HA gene [Presence] in Nasopharynx by NAA with probe detection	M
LOINC	80590-3	Influenza virus A H3 HA gene [Presence] in Nasopharynx by NAA with probe detection	M
LOINC	80591-1	Influenza virus B NS gene [Presence] in Nasopharynx by NAA with probe detection	M
LOINC	82166-0	Influenza virus A RNA [Presence] in Nasopharynx by NAA with non-probe detection	M

Code type	Code	Long Name	Test Type
LOINC	82167-8	Influenza virus A H1 RNA [Presence] in Nasopharynx by NAA with non-probe detection	M
LOINC	82168-6	Influenza virus A H1 2009 pandemic RNA [Presence] in Nasopharynx by NAA with non-probe detection	M
LOINC	82169-4	Influenza virus A H3 RNA [Presence] in Nasopharynx by NAA with non-probe detection	M
LOINC	82170-2	Influenza virus B RNA [Presence] in Nasopharynx by NAA with non-probe detection	M
LOINC	82461-5	Influenza virus A and B and H1 2009 pandemic RNA [Identifier] in Upper respiratory specimen by NAA with probe detection	M
LOINC	85477-8	Influenza virus A RNA [Presence] in Upper respiratory specimen by NAA with probe detection	M
LOINC	85478-6	Influenza virus B RNA [Presence] in Upper respiratory specimen by NAA with probe detection	M
LOINC	85821-7	Influenza virus B Victoria lineage Ag [Presence] in Isolate by Hemagglutination inhibition	Ag
LOINC	86318-3	Influenza virus B Yamagata lineage Ag [Presence] in Isolate by Hemagglutination inhibition	Ag
LOINC	86565-9	Influenza virus A Ag [Presence] in Tissue by Immunofluorescence	Ag
LOINC	86568-3	Influenza virus A RNA [Presence] in Cerebral spinal fluid by NAA with probe detection	M
LOINC	86569-1	Influenza virus A RNA [Presence] in Tissue by NAA with probe detection	M
LOINC	86571-7	Influenza virus B RNA [Presence] in Cerebral spinal fluid by NAA with probe detection	M

Code type	Code	Long Name	Test Type
LOINC	86572-5	Influenza virus B RNA [Presence] in Tissue by NAA with probe detection	M
LOINC	88193-8	Influenza virus A RNA [Presence] in Cornea or Conjunctiva by NAA with probe detection	M
LOINC	88194-6	Influenza virus B Ag [Presence] in Tissue by Immunofluorescence	Ag
LOINC	88195-3	Influenza virus B RNA [Presence] in Cornea or Conjunctiva by NAA with probe detection	M
LOINC	88592-1	Influenza virus B RNA [Presence] in Lower respiratory specimen by NAA with probe detection	M
LOINC	88596-2	Influenza virus B RNA [Presence] in Pericardial fluid by NAA with probe detection	M
LOINC	88599-6	Influenza virus A RNA [Presence] in Lower respiratory specimen by NAA with probe detection	M
LOINC	88600-2	Influenza virus A RNA [Presence] in Pericardial fluid by NAA with probe detection	M
LOINC	88904-8	Influenza virus A Ag [Presence] in Lower respiratory specimen by Immunofluorescence	Ag
LOINC	88905-5	Influenza virus B Ag [Presence] in Lower respiratory specimen by Immunofluorescence	Ag
LOINC	92141-1	Influenza virus B RNA [Presence] in Respiratory specimen by NAA with probe detection	M
LOINC	92142-9	Influenza virus A RNA [Presence] in Respiratory specimen by NAA with probe detection	M
LOINC	92808-5	Influenza virus A H3 RNA [Presence] in Upper respiratory specimen by NAA with probe detection	M
LOINC	92809-3	Influenza virus A H1 RNA [Presence] in Upper respiratory specimen by NAA with probe detection	M

Code type	Code	Long Name	Test Type
LOINC	92976-0	Influenza virus B RNA [Presence] in Lower respiratory specimen by NAA with non-probe detection	M
LOINC	92977-8	Influenza virus A RNA [Presence] in Lower respiratory specimen by NAA with non-probe detection	M
LOINC	94394-4	Influenza virus A H3 RNA [Presence] in Lower respiratory specimen by NAA with probe detection	M
LOINC	94395-1	Influenza virus A H1 2009 pandemic RNA [Presence] in Lower respiratory specimen by NAA with probe detection	M
LOINC	94396-9	Influenza virus A H1 RNA [Presence] in Lower respiratory specimen by NAA with probe detection	M
LOINC	99623-1	Influenza virus A N1 RNA [Presence] in Specimen by NAA with probe detection	M
LOINC	100343-3	Influenza virus B RNA [Presence] in Saliva (oral fluid) by NAA with probe detection	M
LOINC	100344-1	Influenza virus A RNA [Presence] in Saliva (oral fluid) by NAA with probe detection	M
LOINC	101293-9	Influenza virus A H1 2009 pandemic RNA [Presence] in Throat by NAA with non-probe detection	M
LOINC	100973-7	Influenza virus A RNA [Presence] in Nose by NAA with non-probe detection	M
LOINC	101292-1	Influenza virus A RNA [Presence] in Throat by NAA with non-probe detection	M
LOINC	101423-2	Influenza virus A H1 RNA [Presence] in Respiratory system specimen by NAA with probe detection	M
LOINC	101424-0	Influenza virus A H3 RNA [Presence] in Respiratory system specimen by NAA with probe detection	M
LOINC	101294-7	Influenza virus A H3 RNA [Presence] in Throat by NAA with non-probe detection	M

Code type	Code	Long Name	Test Type
LOINC	101295-4	Influenza virus B RNA [Presence] in Throat by NAA with non-probe detection	M
LOINC	100974-5	Influenza virus B RNA [Presence] in Nose by NAA with non-probe detection	M
LOINC	103787-8	Influenza A H3N2V RNA [Presence] in Specimen by NAA with probe detection	M
LOINC	101983-5	Influenza virus A+B RNA [Presence] in Respiratory system specimen by NAA with probe detection	M

Ag, antigen; cDNA, complementary deoxyribonucleic acid; CPT, current procedural terminology; EIA, enzyme immunoassay; ELISA, enzyme-linked immunosorbent assay; FIA, fluorescence immunoassay; ID, immune diffusion; IMCA, immunochemiluminometric assay; LIONC, Logical Observation Identifiers Names and Codes; NAA, nucleic acid amplification; M, molecular detection; RNA, ribonucleic acid.

Supplementary Table 4. List of CVX, CPT, and NDC codes used to identify COVID-19 vaccines from the EHR and linked claims datasets

Manufacturer	CPT	CVX	NDC	ICD-10-PCS
AstraZeneca	91302, 0021A, 0022A	210	00310-1222-10, 00310-1222-15	
Janssen	91303, 0031A, 0034A	212	59676-0580-05, 59676-0580-15	
Moderna	91301, 91306, 91309, 91311, 91313, 91314, 91316, 91321, 91322, 0011A, 0012A, 0013A, 0064A, 0091A, 0092A, 0093A, 0094A, 0111A, 0112A, 0113A, 0134A, 0141A, 0142A, 0144A, 0164A	207, 221, 227, 228, 229, 230, 311, 312, 519	61434-0043-02, 80777-0100-11, 80777-0100-15, 80777-0100-98, 80777-0100-99, 80777-0102-01, 80777-0102-04, 80777-0102-93, 80777-0102-95, 80777-0102-96, 80777-0273-10, 80777-0273-15, 80777-0273-98, 80777-0273-99, 80777-0275-05, 80777-0275-99, 80777-0277-05, 80777-0277-99, 80777-0279-05, 80777-0279-99, 80777-0280-05, 80777-0280-99, 80777-0282-05, 80777-0282-99, 80777-0283-02, 80777-0283-99, 80777-0287-07, 80777-0287-92	
Novavax	91304, 0041A, 0042A, 0044A	211, 313	80631-0100-01, 80631-0100-10, 80631-0102-01, 80631-0105-01, 80631-0105-02, 80631-1000-01	
Pfizer	91317, 91318, 91319, 91320, 0121A, 0151A, 0171A, 0172A, 0173A , 91300, 91305, 91307, 91308, 91312, 91315, 0001A, 0002A, 0003A, 0004A, 0051A, 0052A, 0053A, 0054A, 0071A, 0072A, 0073A, 0074A, 0081A, 0082A, 0083A, 0124A, 0154A	219, 300, 301, 302, 308, 309, 310, 520, 208, 217, 218	00069-1000-01, 00069-1000-02, 00069-1000-03, 00069-2025-01, 00069-2025-10, 00069-2025-25, 00069-2362-01, 00069-2362-10, 00069-2392-01, 00069-2392-10, 59267-0078-01, 59267-0078-02, 59267-0078-04, 59267-0304-01, 59267-0304-02, 59267-0565-01, 59267-0565-02, 59267-0609-01, 59267-0609-02, 59267-1000-01, 59267-1000-02, 59267-1000-03, 59267-1025-01, 59267-1025-02, 59267-1025-03, 59267-1025-04, 59267-1055-01, 59267-1055-02, 59267-1055-04, 59267-1404-01, 59267-1404-02, 59267-4315-01, 59267-4315-02, 59267-4331-01, 59267-4331-02	

Sanofi	91310, 0104A	225, 226	49281-0618-20, 49281-0618-78	
Not Specified	M0201	213		XW013S6, XW013T6, XW013U6, XW023S6, XW023T6, XW023U6

CPT, current procedural terminology; CVX, vaccine administered code set; EHR, electronic health record; ICD, international classification of diseases; NDC, National Drug Code.

Supplementary Table 5. Summary of statistical analyses.

Analysis	Description	Weighting Variables	Multivariable Model Covariates
Descriptive Analysis			
Patient demographic and clinical characteristics	Descriptive statistics for covariates by case status, vaccine type, and case status by vaccine type; SMDs	N/A	N/A
Unadjusted Analysis			
Unadjusted ORs 95% CIs	ORs, unweighted, no covariates	N/A	N/A
Primary Analysis			

Analysis	Description	Weighting Variables	Multivariable Model Covariates
Doubly robust analysis: rVEs and 95% CIs adjusted using IPTW and multivariable regression modeling	rVE, weighted, covariate adjusted	*A priori*: Age (as spline), sex, region, Test Index Date* (as spline), COVID-19 vaccination history Based on SMD: week of vaccination, test type, payer, mean CCI score, endocrine disorders, heart disease and related conditions, metabolic disorders, weakened immune system, mean number of high-risk conditions, number of inpatient admissions, number of ER visits	*A priori*: Age (as spline), sex, region, Test Index Date* (as spline), COVID-19 vaccination history Based on SMD: None
Sensitivity Analyses			

Analysis	**Description**	**Weighting Variables**	**Multivariable Model Covariates**
1. Doubly robust analysis including propensity-to-be-tested scores as a covariate	rVE, weighted, covariate adjusted	*A priori*: Age (as spline), sex, region, Test Index Date* (as spline), COVID-19 vaccination history Based on SMD: week of vaccination, test type, payer, mean CCI score, endocrine disorders, heart disease and related conditions, metabolic disorders, weakened immune system, mean number of high-risk conditions, number of inpatient admissions, number of ER visits	*A priori*: IPTW weight, age (as spline), sex, region, Test Index Date* (as spline), COVID-19 vaccination history Based on SMD: None

Analysis	Description	Weighting Variables	Multivariable Model Covariates
2. Doubly robust analysis including exact matching on the week of the Test Index Date	rVE, weighted, covariate adjusted	*A priori*: Age (as spline), sex, region, COVID-19 vaccination history Based on SMD: week of vaccination, test type, payer, mean CCI score, endocrine disorders, heart disease and related conditions, metabolic disorders, mean number of high-risk conditions, number of inpatient admissions, number of ER visits	*A priori*: IPTW weight, age (as spline), sex, region, COVID-19 vaccination history Based on SMD: None
Subgroup Analyses - Age			
1. Doubly robust analysis with cases limited to pediatric patients (aged 6 months – 17 years)	rVE, weighted, covariate adjusted	*A priori:* Age (as spline), sex, region, Test Index Date* (as spline), COVID-19 vaccination history Based on SMD: test type, payer, number of inpatient admissions, number of ER visits.	*A priori*: IPTW weight, age (as spline), sex, region, Test Index Date* (as spline), COVID-19 vaccination history Based on SMD: number of inpatient admissions

Analysis	Description	Weighting Variables	Multivariable Model Covariates
2. Doubly robust analysis with cases limited to adult patients (aged 18–64 years)	rVE, weighted, covariate adjusted	*A priori*: Age (as spline), sex, region, Test Index Date* (as spline), COVID-19 vaccination history Based on SMD: week of vaccination date, test type, payer, number of inpatient admissions, number of ER visits	*A priori*: IPTW weight, age (as spline), sex, region, Test Index Date* (as spline), COVID-19 vaccination history Based on SMD: None
3. Doubly robust analysis with cases limited to patients aged 4–64 years	rVE, weighted, covariate adjusted	*A priori*: Age (as spline), sex, region, Test Index Date* (as spline), COVID-19 vaccination history Based on SMD: Test type, payer, CCI score, endocrine disorders, heart disease and related conditions, metabolic disorders, mean number of high-risk conditions, number of inpatient admissions, number of ER visits	*A priori*: IPTW weight, age (as spline), sex, region, Test Index Date* (as spline), COVID-19 vaccination history Based on SMD: None

Analysis	Description	Weighting Variables	Multivariable Model Covariates
Subgroup Analyses – Pediatric Subpopulations			
1. Doubly robust analysis limited to pediatric patients (aged 6 months–8 years)	rVE, weighted, covariate adjusted	*A priori*: Age (as spline), sex, region, Test Index Date* (as spline), COVID-19 vaccination history Based on SMD: test type, payer, number of inpatient admissions, number of ER visits.	*A priori*: IPTW weight, age (as spline), sex, region, Test Index Date* (as spline), COVID-19 vaccination history Based on SMD: None
2. Doubly robust analysis limited to pediatric patients (aged 9–17 years)	rVE, weighted, covariate adjusted	*A priori*: Age (as spline), sex, region, Test Index Date* (as spline), COVID-19 vaccination history Based on SMD: test type, payer, number of inpatient admissions	*A priori*: IPTW weight, age (as spline), sex, region, Test Index Date* (as spline), COVID-19 vaccination history Based on SMD: None
Subgroup Analyses – Influenza Type			

Analysis	Description	Weighting Variables	Multivariable Model Covariates
1. Doubly robust analysis with cases limited to influenza A, all controls included	rVE, weighted, covariate adjusted	*A priori*: Age (as spline), sex, region, Test Index Date* (as spline), COVID-19 vaccination history Based on SMD: week of vaccination, test type, payer, mean CCI score, endocrine disorders, heart disease and related conditions, metabolic disorders, weakened immune system, mean number of high-risk conditions, number of inpatient admissions, number of ER visits	*A priori*: IPTW weight, age (as spline), sex, region, Test Index Date* (as spline), COVID-19 vaccination history Based on SMD: None

Analysis	Description	Weighting Variables	Multivariable Model Covariates
2. Doubly robust analysis with cases limited to influenza B, all controls included	rVE, weighted, covariate adjusted	*A priori*: Age (as spline), sex, region, Test Index Date* (as spline), COVID-19 vaccination history Based on SMD: week of vaccination, test type, payer, mean CCI score, endocrine disorders, heart disease and related conditions, metabolic disorders, weakened immune system, mean number of high-risk conditions, number of inpatient admissions, number of ER visits	*A priori*: IPTW weight, age (as spline), sex, region, Test Index Date* (as spline), COVID-19 vaccination history Based on SMD: None

Analysis	Description	Weighting Variables	Multivariable Model Covariates
3. Doubly robust analysis with cases limited to influenza B, all controls included (matched on week of Test Index Date)	rVE, weighted, covariate adjusted	*A priori*: Age (as spline), sex, region, COVID-19 vaccination history Based on SMD: week of vaccination, test type, payer, CCI score, endocrine disorders, heart disease and related conditions, liver disorders, metabolic disorders, weakened immune system, number of high-risk conditions, number of inpatient admissions, number of ER visits	*A priori*: IPTW weight, age (as spline), sex, region, COVID-19 vaccination history Based on SMD: None

Analysis	Description	Weighting Variables	Multivariable Model Covariates
4. Doubly robust analysis with cases limited to influenza B, all controls included, pediatric (aged 6 months–17 years)	rVE, weighted, covariate adjusted	*A priori*: Age (as spline), sex, region, Test Index Date* (as spline), COVID-19 vaccination history Based on SMD: week of vaccination, test type, payer, number of inpatient admissions, number of ER visits	*A priori*: IPTW weight, age (as spline), sex, region, Test Index Date* (as spline), COVID-19 vaccination history Based on SMD: Number of inpatient admissions
Subgroup Analyses – Tested in the Outpatient Setting			

Analysis	Description	Weighting Variables	Multivariable Model Covariates
1. Doubly robust analysis limited to patients tested in the outpatient setting (aged 6 months–64 years)	rVE, weighted, covariate adjusted	*A priori*: Age (as spline), Sex, Region, Test Index Date (as spline), COVID Vaccination History Based on SMD: test type, payer, mean CCI score, endocrine disorders, heart disease and related conditions, metabolic disorders, mean number of high-risk conditions, number of inpatient admissions, number of ER visits	*A priori*: IPTW weight, age (as spline), Sex, Region, Test Index Date (as spline), COVID Vaccination History Based on SMD: None
2. Doubly robust analysis limited to patients tested in the outpatient setting (aged 6 months–17 years)	rVE, weighted, covariate adjusted	*A priori*: Age (as spline), sex, region, Test Index Date* (as spline), COVID-19 vaccination history Based on SMD: test type, payer, number of inpatient admissions, number of ER visits	*A priori*: IPTW weight, age (as spline), sex, region, Test Index Date* (as spline), COVID-19 vaccination history Based on SMD: number of inpatient admissions

Analysis	Description	Weighting Variables	Multivariable Model Covariates
3. Doubly robust analysis limited to patients tested in the outpatient setting (aged 18–64 years)	rVE, weighted, covariate adjusted	*A priori*: Age (as spline), sex, region, Test Index Date* (as spline), COVID-19 vaccination history Based on SMD: week of vaccination date, test type, payer, number of inpatient admissions, number of ER visits	*A priori*: IPTW weight, age (as spline), sex, region, Test Index Date* (as spline), COVID-19 vaccination history Based on SMD: None
Subgroup Analyses – High Risk			

Analysis	Description	Weighting Variables	Multivariable Model Covariates
1. Doubly robust analysis limited to patients with high-risk conditions (aged 6 months–64 years)	rVE, weighted, covariate adjusted	*A priori*: Age (as spline), sex, region, Test Index Date* (as spline), COVID-19 vaccination history Based on SMD: Week of vaccination, test type, payer, CCI score, neurologic and neurodevelopmental conditions, endocrine disorders, heart disease and related conditions, metabolic disorders, mean number of high-risk conditions, number of inpatient admissions, number of ER visits	*A priori*: IPTW weight, age (as spline), sex, region, Test Index Date* (as spline), COVID-19 vaccination history Based on SMD: None

Analysis	Description	Weighting Variables	Multivariable Model Covariates
2. Doubly robust analysis limited to patients with high-risk conditions (aged 5–64 years)	rVE, weighted, covariate adjusted	*A priori*: Age (as spline), sex, region, Test Index Date* (as spline), COVID-19 vaccination history Based on SMD: Test type, payer, asthma, endocrine disorders, heart disease and related conditions, metabolic disorders, mean number of high-risk conditions, number of inpatient admissions, number of ER visits	*A priori*: IPTW weight, age (as spline), sex, region, Test Index Date* (as spline), COVID-19 vaccination history Based on SMD: None
3. Doubly robust analysis limited to patients with high-risk conditions (aged 18–64 years)	rVE, weighted, covariate adjusted	*A priori*: Age (as spline), sex, region, Test Index Date* (as spline), COVID-19 vaccination history Based on SMD: week of vaccination date, test type, payer, number of inpatient admissions, number of ER visits	*A priori*: IPTW weight, age (as spline), sex, region, Test Index Date* (as spline), COVID-19 vaccination history Based on SMD: None

* “Test Index Date” refers to the calendar time between the start of the influenza season and the Test Index.

CCI, Charlson Comorbidity Index; CI, confidence interval; ER, emergency room; IPTW, inverse probability of treatment weighting; OR, odds ratio; rVE, relative vaccine effectiveness; SMD, standardized mean difference.

Supplementary Table 6. High-risk condition categories

High-risk category	Conditions
Asthma	Mild, moderate, severe, and other asthma
Neurologic and neurodevelopmental conditions	Pervasive and specific developmental disorders, tic disorder, cerebral palsy, monosomies and deletions from the autosomes, balanced rearrangements and structural markers, Turner syndrome, other sex chromosome abnormalities, epilepsy, Huntington's, multiple sclerosis, myopathies, spinal cord injury, Parkinson's disease, Parkinsonism, dementia, hydrocephalus
Blood disorders	Nutritional anemias, hemolytic anemias, aplastic and other anemias, and other bone marrow failure syndromes, coagulation defects, purpura and other hemorrhagic conditions, other disorders of blood and blood-forming organs
Chronic lung disease	COPD, bronchiectasis, respiratory conditions due to external agents, chronic pulmonary oedema, chronic eosinophilic pneumonia, interstitial pulmonary disease, cystic fibrosis
Endocrine disorders	Diabetes mellitus, thyroid disorders, other endocrine disorders
Heart disease and related conditions	Acute rheumatic fever, chronic rheumatic heart disease, hypertensive diseases, ischemic heart diseases (including angina and myocardial infarction), pulmonary heart disease and diseases of pulmonary circulation, pericarditis and other diseases of pericardium, endocarditis, myocarditis, non-rheumatic valve disorders, cardiomyopathy, conduction disorders, cardiac arrhythmias, cardiac arrest, heart failure, other forms of heart disease, cerebrovascular disease (other than stroke), peripheral vascular disease, and other diseases of arteries, arterioles, and capillaries, other diseases of veins, lymphatic vessels, and lymph nodes, other disorders of the circulatory system, congenital malformations of the circulatory system
Renal disease	Chronic kidney disease, end stage renal disease, kidney failure, kidney transplant, dialysis-related diagnoses, chronic nephrotic syndrome, unspecified nephrotic syndrome, renal osteodystrophy
Liver disorders	Alcoholic liver disease, toxic liver disease, hepatic failure, chronic hepatitis, fibrosis and cirrhosis of liver, other liver diseases, liver transplant status
Metabolic disorders	Disorders of amino-acid metabolism, carbohydrate metabolism, sphingolipid metabolism, glycosaminoglycan metabolism, glycoprotein metabolism, lipoprotein metabolism, purine and pyrimidine metabolism, porphyrin and bilirubin metabolism, and mineral metabolism, amyloidosis, disorders of fluid, electrolyte and acid-base balance, other and unspecified metabolic disorders, Leigh's disease, Reye's syndrome, hereditary optic atrophy, Kearns-Sayre syndrome
Obesity	BMI $\geq$40 kg/m^2 (BMI values or diagnosis codes)

Weakened immune system	HIV, malignancies, or a chronic condition requiring chronic corticosteroids or other drugs that suppress the immune system
Stroke	Hemorrhagic stroke, ischemic stroke, transient ischemic attack

BMI, body mass index; CCI, Charlson Comorbidity Index; COPD, chronic obstructive pulmonary disease.

Supplementary Table 7. Unadjusted ORs of QIVc vs. QIVe in prevention of test-confirmed influenza among outpatient subpopulations during the 2023–2024 influenza season in the US

Analysis	Age	Unadjusted OR (95% CI)
Main	6 month–64 years	0.74 (0.71–0.78)
Sensitivity analyses		
Propensity to be tested	6 month–64 years	NA as analysis required adjustment
Matched on test week	6 month–64 years	0.75 (0.71–0.79)
Age subgroups		
Pediatric	6 month–17 years	0.84 (0.79–0.90)
Infants/children	6 month–8 years	0.87 (0.80–0.95)
Children/adolescent	9–17 years	0.78 (0.70–0.87)
Adult	18–64 years	0.79 (0.73–0.85)
Influenza type		
Influenza A only	6 month–64 years	0.79 (0.74–0.83)
Influenza B only	6 month–64 years	0.55 (0.50–0.61)
High-risk subgroups		
All	6 month–64 years	0.78 (0.73–0.83)
Children/adults	5–64 years	0.75 (0.70–0.81)
Adult	18–64 years	0.81 (0.74–0.88)
Outpatient		
All	6 month–64 years	0.74 (0.70–0.78)
Pediatric	6 month–17 years	0.83 (0.77–0.89)
Adult	18–64 years	0.78 (0.72–0.84)

CI, confidence interval; NA, not applicable; OR, odds ratio; QIVc, cell-based quadrivalent influenza vaccine, QIVe, egg-based quadrivalent influenza vaccine; US, United States.

Supplementary Table 8. Model input data for analysis of aVE of QIVe and influenza burden averted (2023–2024 influenza season in the US)

	0–4 years	5–17 years	18–49 years	50–64 years
Vaccine data				
aVE QIVe, % (95% CI)[a]	52 (31–67)	59 (35–75)	38 (24–50)	16 (0–41)
rVE QIVc vs QIVe, % (95% CI)	19.6 (13.6–25.3)	19.6 (13.6–25.3)	18.5 (12.1–24.5)	18.5 (12.1–24.5)
Vaccine coverage, %[b]	64	55	33	46
Influenza burden and healthcare resource use without vaccination, n (95% CI)				
Symptomatic cases[c]	2,903,633 (2,316,504–4,721,510)	9,287,627 (7,118,757–19,577,782)	16,351,383 (12,094,473–28,147,985)	9,042,884 (6,536,493–19,011,230)
Outpatient visits	1,945,434 (1,423,698–4,721,510)	4,829,566 (3,383,771–10,156,811)	6,050,012 (3,940,361–28,147,985)	3,888,440 (2,457,484–8,502,440)
Hospitalizations	20,243 (16,150–32,916)	25,466 (19,519–53,680)	91,780 (67,886–157,995)	95,897 (69,318–201,609)
ICU admissions	3 864 (2455–7505)	4,839 (2967–12,239)	13,767 (8146–28,439)	15,919 (9205–40,161)
Deaths	268 (66–484)	253 (95–621)	2705 (1565–4465)	5701 (3001–7973)

[a]Data from CDC end-of-season estimates [1]; [b]Percentage vaccinated, taken from CDC FluVaxView Interactive [2]. Percentages are weighted to the U.S. population. Month of vaccination was imputed for respondents with missing month of vaccination data. CIs are half-widths; [c]CDC data on influenza burden [3].

aVE, absolute vaccine effectiveness; CDC, Centers for Disease Control and Prevention; CI, confidence interval; ICU, intensive care unit; QIVc, cell-based quadrivalent influenza vaccine; QIVe, egg-based quadrivalent influenza vaccine; rVE, relative vaccine effectiveness; US, United States.

Supplementary Table 9. Demographics and clinical characteristics of full population by vaccine type and test result (2023–2024 influenza season in the US)

Variable	Overall (*N*=106,779)	QIVc			QIVe		
		Total (*n*=16,869)	Case (*n*=2119)	Control[a] (*n*=14,750)	Total (*n*=89,910)	Case (*n*=14,559)	Control[a] (*n*=75,351)
Age at index date, years							
Mean (SD)	23.5 (21.6)	29.6 (22.3)	24.7 (21.2)	30.3 (22.4)	22.3 (21.2)	18.5 (18.7)	23.0 (21.6)
Median (IQR)	14 (39)	28 (45)	14 (38)	30 (45)	12 (37)	10 (23)	13 (39)
Age group at index date, n (%)							
0–4 years	25,358 (24)	2914 (17)	340 (16)	2574 (17)	22,444 (25)	2844 (20)	19,600 (26)
5–17 years	35,632 (33)	4280 (25)	846 (40)	3434 (23)	31,352 (35)	7409 (51)	23,943 (32)
18–49 years	24,116 (23)	4868 (29)	493 (23)	4375 (30)	19,248 (21)	2506 (17)	16,742 (22)
50–64 years	21,673 (20)	4807 (28)	440 (21)	4367 (30)	16,866 (19)	1800 (12)	15,066 (20)
Sex, n (%)							
Female	61,511 (58)	9990 (59)	1174 (55)	8816 (60)	51,521 (57)	7872 (54)	43,649 (58)
Male	45,268 (42)	6879 (41)	945 (45)	5934 (40)	38,389 (43)	6687 (46)	31,702 (42)
Race, n (%)							
White	23,343 (22)	3846 (23)	404 (19)	3,442 (23)	19,497 (22)	2988 (21)	16,509 (22)
Black	5778 (5)	846 (5)	98 (5)	748 (5)	4932 (5)	747 (5)	4185 (6)
Asian	2563 (2)	616 (4)	73 (3)	543 (4)	1947 (2)	326 (2)	1621 (2)
Other	6156 (6)	936 (6)	115 (5)	821 (6)	5220 (6)	775 (5)	4445 (6)
Unknown/not reported	68,939 (65)	10,625 (63)	1429 (67)	9196 (62)	58,314 (65)	9723 (67)	48,591 (64)
HHS region, n (%)							
Region 1	4024 (4)	546 (3)	86 (4)	460 (3)	3478 (4)	639 (4)	2839 (4)
Region 2	16,868 (16)	2825 (17)	251 (12)	2574 (17)	14,043 (16)	2225 (15)	11,818 (16)

Variable	Overall (*N*=106,779)	QIVc			QIVe		
		Total (*n*=16,869)	Case (*n*=2119)	Control[a] (*n*=14,750)	Total (*n*=89,910)	Case (*n*=14,559)	Control[a] (*n*=75,351)
Region 3	5693 (5)	518 (3)	61 (3)	457 (3)	5175 (6)	824 (6)	4351 (6)
Region 4	29,204 (27)	5252 (31)	712 (34)	4540 (31)	23,952 (27)	4122 (28)	19,830 (26)
Region 5	15,431 (14)	3565 (21)	599 (28)	2966 (20)	11,866 (13)	2174 (15)	9692 (13)
Region 6	6798 (6)	1218 (7)	113 (5)	1105 (7)	5580 (6)	913 (6)	4667 (6)
Region 7	7766 (7)	354 (2)	50 (2)	304 (2)	7412 (8)	1417 (10)	5995 (8)
Region 8	2278 (2)	131 (1)	23 (1)	108 (1)	2147 (2)	372 (3)	1775 (2)
Region 9	17,098 (16)	2268 (13)	209 (10)	2059 (14)	14,830 (16)	1694 (12)	13,136 (17)
Region 10	1619 (2)	192 (1)	15 (1)	177 (1)	1427 (2)	179 (1)	1248 (2)
Week of vaccination date							
Mean (SD)	12.1 (5.4)	11.6 (5.1)	11.4 (4.7)	11.6 (5.2)	12.1 (5.4)	11.9 (4.9)	12.2 (5.5)
Test type, n (%)							
Antigen	16,330 (15%)	2168 (13%)	214 (10%)	1954 (13%)	14,162 (16%)	2288 (16%)	11,874 (16%)
Molecular	23,100 (22%)	4521 (27%)	569 (27%)	3952 (27%)	18,579 (21%)	2842 (20%)	15,737 (21%)
Unknown	67,349 (63%)	10,180 (60%)	1336 (63%)	8844 (60%)	57,169 (64%)	9429 (65%)	47,740 (63%)
Payer on influenza test date, n (%)							
Commercial	37,966 (36)	7385 (44)	831 (39)	6554 (44)	30,581 (34)	4326 (30)	26,255 (35)
Medicaid	25,321 (24)	3847 (23)	485 (23)	3362 (23)	21,474 (24)	3180 (22)	18,294 (24)
Medicare Advantage	1445 (1)	290 (2)	25 (1)	265 (2)	1155 (1)	108 (1)	1047 (1)
Unknown/other	42,047 (39)	5347 (32)	778 (37)	4569 (31)	36,700 (41)	6945 (48)	29,755 (39)
COVID-19 vaccination (prior 6 months), n (%)	3961 (4)	956 (5.7)	79 (3.7)	877 (5.9)	3005 (3.3)	389 (2.7)	2616 (3.5)
Charlson Comorbidity Index							

Variable	Overall (*N*=106,779)	QIVc			QIVe		
		Total (*n*=16,869)	Case (*n*=2119)	Control[a] (*n*=14,750)	Total (*n*=89,910)	Case (*n*=14,559)	Control[a] (*n*=75,351)
Mean (SD)	0.6 (1.2)	0.7 (1.4)	0.6 (1.2)	0.8 (1.5)	0.6 (1.2)	0.4 (0.9)	0.6 (1.2)
Median (IQR)	0 (1)	0 (1)	0 (1)	0 (1)	0 (1)	0 (1)	0 (1)
High-risk conditions, n (%)							
Asthma	16,818 (16%)	2618 (16%)	339 (16%)	2,279 (15%)	14200 (16%)	2,256 (15%)	11,944 (16%)
Neurologic and neurodevelopmental conditions	9768 (9%)	1272 (8%)	182 (9%)	1090 (7%)	8496 (9%)	1351 (9%)	7145 (9%)
Blood disorders	13,029 (12%)	2520 (15%)	273 (13%)	2247 (15%)	10,509 (12%)	1217 (8%)	9292 (12%)
Chronic lung disease	4158 (4%)	823 (5%)	60 (3%)	763 (5%)	3335 (4%)	296 (2%)	3039 (4%)
Endocrine disorders	17,957 (17%)	3771 (22%)	361 (17%)	3410 (23%)	14,186 (16%)	1655 (11%)	12,531 (17%)
Heart disease and related conditions	24,321 (23%)	5043 (30%)	472 (22%)	4571 (31%)	19,278 (21%)	2170 (15%)	17,108 (23%)
Kidney diseases	2670 (3%)	571 (3%)	60 (3%)	511 (3%)	2099 (2%)	204 (1%)	1895 (3%)
Liver disorders	4001 (4%)	877 (5%)	84 (4%)	793 (5%)	3124 (3%)	303 (2%)	2821 (4%)
Metabolic disorders	24,963 (23%)	5220 (31%)	525 (25%)	4695 (32%)	19,743 (22%)	2306 (16%)	17,437 (23%)
Obesity, BMI ≥40 kg/m^2	5039 (5%)	892 (5%)	85 (4%)	807 (5%)	4147 (5%)	450 (3%)	3697 (5%)
Weakened immune system	5769 (5%)	1288 (8%)	146 (7%)	1142 (8%)	4481 (5%)	531 (4%)	3950 (5%)
Stroke	1625 (2%)	337 (2%)	27 (1%)	310 (2%)	1288 (1%)	115 (1%)	1173 (2%)
≥1 High-risk condition; n (%)	57,139 (54)	10,047 (60)	1136 (54)	8911 (60)	47,092 (52)	6625 (46)	40,467 (54)
Baseline healthcare resource utilization							
No. of inpatient admissions, n (%)							
0	29,547 (28%)	5417 (32%)	616 (29%)	4,801 (33%)	24130 (27%)	3822 (26%)	20,308 (27%)

Variable	Overall (*N*=106,779)	QIVc			QIVe		
		Total (*n*=16,869)	Case (*n*=2119)	Control[a] (*n*=14,750)	Total (*n*=89,910)	Case (*n*=14,559)	Control[a] (*n*=75,351)
≥1	9077 (9%)	1676 (10%)	159 (8%)	1517 (10%)	7401 (8%)	718 (5%)	6,683 (9%)
Unknown	68,155 (64%)	9776 (58%)	1344 (63%)	8432 (57%)	58379 (65%)	10,019 (69%)	48,360 (64%)
No. of ER visits, n (%)							
0	20,275 (19%)	4031 (24%)	469 (22%)	3562 (24%)	16,244 (18%)	2718 (19%)	13,526 (18%)
≥1	27,115 (25%)	4262 (25%)	477 (23%)	3785 (26%)	22,853 (25%)	2902 (20%)	19,951 (26%)
Unknown	59,389 (56%)	8576 (51%)	1173 (55%)	7403 (50%)	50,813 (57%)	8939 (61%)	41,874 (56%)

[a]Within 6 months prior to Test Index Date; [b]Neurologic and neurodevelopmental conditions; [c]Heart disease and related conditions; [d]BMI ≥40 kg/m^2.

HHS region 1 includes Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, Vermont, region 2 includes New Jersey, New York, Puerto Rico, the Virgin Islands, region 3 includes Delaware, District of Columbia, Maryland, Pennsylvania Virginia, West Virginia, region 4 includes Alabama, Florida, Georgia, Kentucky, Mississippi, North Carolina, South Carolina, Tennessee, region 5 includes Illinois, Indiana, Michigan, Minnesota, Ohio, Wisconsin, region 6 includes Arkansas, Louisiana, New Mexico, Oklahoma, Texas, region 7 includes Iowa, Kansas, Missouri, Nebraska, region 8 includes Colorado, Montana, North Dakota, South Dakota, Utah, Wyoming, region 9 includes Arizona, California, Hawaii, Nevada, American Samoa, Commonwealth of the Northern Mariana Islands, Federated States of Micronesia, Guam, Marshall Islands, Republic of Palau and region 10 includes Alaska, Idaho, Oregon, Washington.

BMI, body mass index; ER, emergency room; HHS, US. Department of Health and Human Services; IQR, interquartile range; QIVc, cell-based quadrivalent influenza vaccine; QIVe, egg-based quadrivalent influenza vaccine; SMD, standardized mean difference; SD, standard deviation; US, United States.

Supplementary Table 10. Demographics and clinical characteristics of high-risk sub-population by vaccine type and test result (2023–2024 influenza season in the US)

Variable	Total	QIVc		QIVe	
		Case	Control	Case	Control
Age at index date					
Mean (SD)	32 (22.8)	32.8 (22.2)	38.6 (21.3)	26.1 (21.9)	31.5 (22.9)
Median (IQR)	34 (47)	37 (44)	45 (40)	15 (41)	33 (47)
Age group at index date, n (%)					
0–4 years	9137 (16)	118 (10)	905 (10)	992 (15)	7122 (18)
5–17 years	13,469 (24)	329 (29)	1306 (15)	2564 (39)	9270 (23)
18–49 years	15,335 (27)	300 (26)	2831 (32)	1495 (23)	10,709 (26)
50–64 years	19,198 (34)	389 (34)	3869 (43)	1574 (24)	13,366 (33)
Sex, n (%)					
Female	33,650 (59)	623 (55)	5397 (61)	3627 (55)	24,003 (59)
Male	23,489 (41)	513 (45)	3514 (39)	2998 (45)	16,464 (41)
Race, n (%)					
White	13,569 (24)	251 (22)	2302 (26)	1429 (22)	9587 (24)
Black	3611 (6)	64 (6)	523 (6)	418 (6)	2606 (6)
Asian	1448 (3)	38 (3)	391 (4)	155 (2)	864 (2)
Other	3424 (6)	68 (6)	547 (6)	402 (6)	2407 (6)
Not reported	35,087 (61)	715 (63)	5148 (58)	4221 (64)	25,003 (62)
HHS region, n (%)					
Region 1	1912 (3)	35 (3)	240 (3)	273 (4)	1364 (3)
Region 2	8528 (15)	142 (13)	1420 (16)	1003 (15)	5963 (15)
Region 3	3217 (6)	41 (4)	333 (4)	395 (6)	2448 (6)

Region 4	15,953 (28)	387 (34)	2666 (30)	1900 (29)	11,000 (27)
Region 5	7892 (14)	275 (24)	1630 (18)	937 (14)	5050 (12)
Region 6	3883 (7)	71 (6)	772 (9)	442 (7)	2598 (6)
Region 7	3961 (7)	31 (3)	207 (2)	621 (9)	3102 (8)
Region 8	1005 (2)	10 (1)	49 (1)	136 (2)	810 (2)
Region 9	10,058 (18)	133 (12)	1483 (17)	849 (13)	7593 (19)
Region 10	730 (1)	11 (1)	111 (1)	69 (1)	539 (1)
Week of vaccination date					
Mean (SD)	11.6 (5.1)	10.9 (4.4)	11.1 (5.0)	11.5 (4.7)	11.7 (5.2)
Test type, n (%)					
Antigen	9008 (16)	136 (12)	1332 (15)	1059 (16)	6481 (16)
Molecular	12,379 (22)	317 (28)	2516 (28)	1304 (20)	8242 (20)
Unknown	35,752 (63)	683 (60)	5063 (57)	4262 (64)	25,744 (64)
Payer at tax index date, n (%)					
Commercial	22,126 (39)	479 (42)	4114 (46)	2249 (34)	15,284 (38)
Medicaid	15,106 (26)	288 (25)	2364 (27)	1599 (24)	10,855 (27)
Medicare Advantage	1378 (2)	24 (2)	252 (3)	104 (2)	998 (2)
Unknown/other	18,529 (32)	345 (30)	2181 (24)	2673 (40)	13,330 (33)
COVID-19 vaccine[a], n (%)	2733 (5)	60 (5)	579 (6)	253 (4)	1841 (5)
Charlson Comorbidity Index					
Mean (SD)	1.1 (1.5)	1.0 (1.5)	1.2 (1.7)	0.9 (1.2)	1.1 (1.5)
Median (IQR)	1 (1)	1 (1)	1 (2)	1 (1)	1 (1)
High-risk conditions, n (%)					
Asthma	16,818 (29)	339 (30)	2279 (26)	2256 (34)	11,944 (30)
Neurologic conditions[b]	9768 (17)	182 (16)	1090 (12)	1351 (20)	7145 (18)

Blood disorders	13,029 (23)	273 (24)	2247 (25)	1217 (18)	9292 (23)
Chronic lung disease	4158 (7)	60 (5)	763 (9)	296 (4)	3039 (8)
Endocrine disorders	17,957 (31)	361 (32)	3410 (38)	1655 (25)	12,531 (31)
Heart disease[c]	24,321 (43)	472 (42)	4571 (51)	2170 (33)	17,108 (42)
Kidney diseases	2670 (5)	60 (5)	511 (6)	204 (3)	1895 (5)
Liver disorders	4001 (7)	84 (7)	793 (9)	303 (5)	2821 (7)
Metabolic disorders	24,963 (44)	525 (46)	4695 (53)	2306 (35)	17,437 (43)
Obesity[d]	5039 (9)	85 (7)	807 (9)	450 (7)	3697 (9)
Weak immune system	5769 (10)	146 (13)	1142 (13)	531 (8)	3950 (10)
Stroke	1625 (3)	27 (2)	310 (3)	115 (2)	1173 (3)
≥1 High-risk condition; n (%)	57,139 (100)	1136 (100)	8911 (100)	6625 (100)	40,467 (100)
Baseline healthcare resource utilization					
No. of inpatient admissions, n (%)					
0	17,299 (30)	371 (33)	3272 (37)	1896 (29)	11,760 (29)
≥1	6937 (12)	138 (12)	1281 (14)	520 (8)	4998 (12)
Unknown	32,903 (58)	627 (55)	4358 (49)	4209 (64)	23,709 (59)
No. of ER visits, n (%)					
0	11,046 (19)	262 (23)	2299 (26)	1240 (19)	7245 (18)
≥1	18,374 (32)	331 (29)	2915 (33)	1742 (26)	13,386 (33)
Unknown	27,719 (49)	543 (48)	3697 (41)	3643 (55)	19,836 (49)

[a]Within 6 months prior to Test Index Date; [b]Neurologic and neurodevelopmental conditions; [c]Heart disease and related conditions; [d]BMI ≥40 kg/m^2.

HHS region 1 includes Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, Vermont, region 2 includes New Jersey, New York, Puerto Rico, the Virgin Islands, region 3 includes Delaware, District of Columbia, Maryland, Pennsylvania Virginia, West

Virginia, region 4 includes Alabama, Florida, Georgia, Kentucky, Mississippi, North Carolina, South Carolina, Tennessee, region 5 includes Illinois, Indiana, Michigan, Minnesota, Ohio, Wisconsin, region 6 includes Arkansas, Louisiana, New Mexico, Oklahoma, Texas, region 7 includes Iowa, Kansas, Missouri, Nebraska, region 8 includes Colorado, Montana, North Dakota, South Dakota, Utah, Wyoming, region 9 includes Arizona, California, Hawaii, Nevada, American Samoa, Commonwealth of the Northern Mariana Islands, Federated States of Micronesia, Guam, Marshall Islands, Republic of Palau and region 10 includes Alaska, Idaho, Oregon, Washington.

BMI, body mass index; ER, emergency room; HHS, US. Department of Health and Human Services; IQR, interquartile range; QIVc, cell-based quadrivalent influenza vaccine; QIVe, egg-based quadrivalent influenza vaccine; SMD, standardized mean difference; SD, standard deviation; US, United States.

Supplementary Table 11. Demographics and clinical characteristics of influenza A cases and influenza B cases by vaccine type (2023–2024 influenza season in the US)

	QIVc		QIVe	
	Influenza A ***n*=1305**	**Influenza B** ***n*=427**	**Influenza A** ***n*=8494**	**Influenza B** ***n*=3950**
Age at index date, years				
Mean (SD)	26.4 (22.1)	19.6 (17.0)	19.6 (19.8)	15.4 (15.2)
Median (IQR)	16 (43)	12 (24)	10 (29)	10 (10)
Age group at index date, n (%)				
6 months–4 years	220 (17)	44 (10)	1825 (21)	644 (16)
5–17 years	460 (35)	240 (56)	3975 (47)	2414 (61)
18–49 years	301 (23)	101 (24)	1401 (16)	665 (17)
50–64 years	324 (25)	42 (10)	1293 (15)	227 (6)
Female, n (%)	725 (56)	234 (55)	4619 (54)	2040 (52)
Race, n (%)				
White	263 (20)	81 (19)	1782 (21)	849 (21)
Black	62 (5)	30 (7)	437 (5)	239 (6)
Asian	52 (4)	15 (4)	191 (2)	103 (3)
Other	84 (6)	22 (5)	517 (6)	202 (5)
Not reported	844 (65)	279 (65)	5567 (66)	2557 (65)
HHS region, n (%)				
Region 1	60 (5)	17 (4)	449 (5)	138 (3)
Region 2	188 (14)	50 (12)	1490 (18)	547 (14)

	QIVc		QIVe	
	Influenza A	**Influenza B**	**Influenza A**	**Influenza B**
	***n*=1305**	***n*=427**	***n*=8494**	***n*=3950**
Region 3	42 (3)	12 (3)	527 (6)	205 (5)
Region 4	317 (24)	120 (28)	2247 (26)	1080 (27)
Region 5	423 (32)	136 (32)	1165 (14)	671 (17)
Region 6	76 (6)	29 (7)	497 (6)	307 (8)
Region 7	21 (2)	14 (3)	657 (8)	487 (12)
Region 8	7 (1)	2 (0)	150 (2)	88 (2)
Region 9	156 (12)	47 (11)	1230 (14)	359 (9)
Region 10	15 (1)	0 (0)	82 (1)	68 (2)
Week of vaccination date, mean (SD)	11.2 (4.5)	11.7 (5.0)	11.6 (4.7)	12.4 (5.3)
Test type, n (%)				
Antigen	147 (11)	34 (8)	1436 (17)	653 (17)
Molecular	415 (32)	93 (22)	2026 (24)	706 (18)
Unknown	743 (57)	300 (70)	5032 (59)	2591 (66)
Payer at Test Index Date, n (%)				
Commercial	553 (42)	177 (41)	2709 (32)	1017 (26)
Medicaid	345 (26)	115 (27)	1949 (23)	1003 (25)
Medicare Advantage	20 (2)	3 (1)	84 (1)	11 (0)
Unknown/other	387 (30)	132 (31)	3752 (44)	1919 (49)
COVID-19 vaccine[a], n (%)	51 (4)	8 (2)	221 (3)	97 (2)
Charlson Comorbidity Index				

	QIVc		QIVe	
	Influenza A	**Influenza B**	**Influenza A**	**Influenza B**
	***n*=1305**	***n*=427**	***n*=8494**	***n*=3950**
Mean (SD)	0.7 (1.3)	0.5 (1.1)	0.5 (1.0)	0.3 (0.7)
Median (IQR)	0 (1)	0 (1)	0 (1)	0 (0)
High-risk conditions, n (%)				
Asthma	223 (17)	78 (18)	1409 (17)	524 (13)
Neurologic conditions[b]	112 (9)	42 (10)	807 (10)	385 (10)
Blood disorders	190 (15)	43 (10)	768 (9)	267 (7)
Chronic lung disease	43 (3)	12 (3)	215 (3)	41 (1)
Endocrine disorders	242 (19)	58 (14)	1063 (13)	319 (8)
Heart disease[c]	340 (26)	65 (15)	1433 (17)	402 (10)
Kidney diseases	44 (3)	9 (2)	141 (2)	29 (1)
Liver disorders	60 (5)	14 (3)	188 (2)	60 (2)
Metabolic disorders	359 (28)	77 (18)	1499 (18)	439 (11)
Obesity[d]	60 (5)	13 (3)	271 (3)	93 (2)
Weak immune system	107 (8)	25 (6)	335 (4)	112 (3)
Stroke	22 (2)	2 (0)	80 (1)	21 (1)
≥1 High-risk condition; n(%)	745 (57)	205 (48)	4100 (48)	1559 (39)
Baseline healthcare resource utilization				
No. of inpatient admissions, n (%)				
0	427 (33)	132 (31)	2349 (28)	1142 (29)
≥1	116 (9)	28 (7)	481 (6)	160 (4)

	QIVc		QIVe	
	Influenza A ***n*=1305**	**Influenza B** ***n*=427**	**Influenza A** ***n*=8494**	**Influenza B** ***n*=3950**
Unknown	762 (58)	267 (63)	5664 (67)	2648 (67)
No. of ER visits, n (%)				
0	326 (25)	93 (22)	1640 (19)	816 (21)
≥1	332 (25)	118 (28)	1872 (22)	795 (20)
Unknown	647 (50)	216 (51)	4982 (59)	2339 (59)

[a]Within 6 months prior to Test Index Date; [b]Neurologic and neurodevelopmental conditions; [c]Heart disease and related conditions; [d]BMI ≥40 kg/m^2

HHS region 1 includes Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, Vermont, region 2 includes New Jersey, New York, Puerto Rico, the Virgin Islands, region 3 includes Delaware, District of Columbia, Maryland, Pennsylvania Virginia, West Virginia, region 4 includes Alabama, Florida, Georgia, Kentucky, Mississippi, North Carolina, South Carolina, Tennessee, region 5 includes Illinois, Indiana, Michigan, Minnesota, Ohio, Wisconsin, region 6 includes Arkansas, Louisiana, New Mexico, Oklahoma, Texas, region 7 includes Iowa, Kansas, Missouri, Nebraska, region 8 includes Colorado, Montana, North Dakota, South Dakota, Utah, Wyoming, region 9 includes Arizona, California, Hawaii, Nevada, American Samoa, Commonwealth of the Northern Mariana Islands, Federated States of Micronesia, Guam, Marshall Islands, Republic of Palau and region 10 includes Alaska, Idaho, Oregon, Washington.

BMI, body mass index; ER, emergency room; HHS, US. Department of Health and Human Services; IQR, interquartile range; QIVc, cell-based quadrivalent influenza vaccine; QIVe, egg-based quadrivalent influenza vaccine; SMD, standardized mean difference; SD, standard deviation; US, United States.

Supplementary Table 12. Location of amino acid substitutions in the HA protein of egg-based vaccine viruses, NH 2023–2024 season [4]

Platform	WHO recommendation	Amino acid changes in HA protein (as compared to cell isolate or original clinical samples)[a]
	A/H1N1	
Egg-based	A/Victoria/4897/2022 (H1N1)pdm09-like virus	F111L, R142K[b], E172K, D187E, D187N, Q223R[b], N287T
Cell-based	A/Wisconsin/67/2022 (H1N1)pdm09-like virus	No changes
	A/H3N2	
Egg-based	A/Darwin/9/2021 (H3N2)-like virus	S46P, S96C, D186N[b], D225G[b]
Cell-based	A/Darwin/6/2021 (H3N2)-like virus;	No changes
	B/Victoria	
Egg-based	B/Austria/1359417/2021 (B/Victoria lineage)-like virus	G141R[b], D194Y, T232I
Cell-based	B/Austria/1359417/2021 (B/Victoria lineage)-like virus	No changes
	B/Yamagata	
Egg-based	B/Phuket/3073/2013 (B/Yamagata lineage)-like virus	V91I, K163E, N197D[b], N197E, N197I, N197K, N197S, T199I, T199N, T260K, G238E[b], S457G
Cell-based	B/Phuket/3073/2013 (B/Yamagata lineage)-like virus	No changes

The table shows data for all viruses that have been through manufacturing as listed in each of the recommendations by the WHO [5].

[a]Amino acid change in at least one wild-type or reassortant vaccine virus identified from a detailed sequence analysis performed by CSL Seqirus [4, 6].

[b]Amino acid changes identified in the HA protein of the specific CVVs used in the standard-dose cell- and egg-based vaccines available in the United States (CVVs used in Fluzone® quadrivalent 2023–2024 formula were taken from the 2023–2024 season prescribing information for Fluzone® high-dose quadrivalent) [7-11].

CVV, candidate vaccine virus; HA, hemagglutinin; NH, Northern Hemisphere; WHO, World Health Organization.

Supplementary Appendix

Appendix 1. Data sources

This analysis was conducted using a dataset provided by HealthVerity that integrates U.S. data from multiple sources of electronic health records (EHR)/electronic medical record (EMR) (henceforth referred to as “EHR"), laboratory, medical claims, and pharmacy claims data. The data available on the results of the influenza tests performed as part of routine inpatient or outpatient care formed the basis of the outcome for this study. Specifically, data sources included:

- Medical claims
  - Waystar medical claims, professional and institutional
    - Source 12: Claims clearinghouse providing electronic claims with an optional link to remittances for over 100 different practice management software vendors.
    - Source 13: Billing and claims clearinghouse providing annual access to over 60 million electronic medical claims and matching remittances. This data represents a national footprint with claims data covering 94,000 healthcare providers, including more than half of Federally Qualified Health Centers (FQHC), and over 5000 unique health insurance carriers.
    - Source 34: Claims clearinghouse providing professional and institutional claims for over 800,000 providers and large volumes of unique specialties.
  - Inovalon closed payer medical claims
    - Inovalon medical claims represent inpatient and outpatient diagnoses, procedures and physician-administered medications. Inovalon captures enrollment/eligibility information as well as treating physician identity, patient/physician geography, and physician visit information. Because closed payer data captures all insurance-related patient transactions, the availability of both common and rare diseases, comorbidities, outcomes tracking, and in-office medication administration is found in this dataset. The diversity of payers in the sample allows following of a patient's journey across multiple payers and potentially from one insurance type to another.
  - Inovalon open medical claims

    - This data provides claims for important specialties such as cardiology, gastroenterology, rheumatology, radiology, obstetrics and gynecology, and psychiatry.
- Pharmacy claims
  - Inovalon closed payer pharmacy claims
    - Inovalon pharmacy data includes retail and specialty pharmacy medications filled over the enrollment/eligibility period. Inovalon captures enrollment/eligibility information as well as prescribing physician identity, patient/physician geography, and drug-related information (drug name, dose, days, etc.). Because closed payer data captures all insurance-related patient transactions, the availability of both common and scarce drug activity, adherence and switching are available.
- Electronic Medical Records
  - Veradigm EHR
    - Veradigm Network EHR Data provides de-identified real-world data from an extensive national population of patients drawn from physician practices using a variety of EHR products. Veradigm Network EHR Data provides information relating to an encounter with a medical professional, for which the provider records details in an electronic version of a patient chart. This includes vitals, patient history, and lab orders and results. This data is sourced from over 20,000 practices across the U.S. ranging from single-provider offices to integrated delivery system providers and both primary and specialty care.
  - Inovalon (formerly Teton Analytics) EMR
    - Drawing from an EMR dataset of over 20 million unique patients, Inovalon EMR provides insights into disease states that pass through a hospital with a unique focus on infectious disease.
  - Source 42 EMR
    - This multi-specialty EMR vendor currently has clinical records for nearly 60 million unique patients and offers both ambulatory and specialty practices EMR data.
- Laboratory data
  - Labcorp lab data

    - Labcorp data includes test information on a wide range of specialty testing services and results for nearly 160 million unique patients. Labcorp provides a wide range of specialty testing services in the areas of COVID-19, women's health, allergy, diagnostic genetics, cardiovascular disease, infectious disease, endocrinology, oncology, coagulation, pharmacogenetics, toxicology, and medical drug monitoring.
- Quest Diagnostics lab data
    - Quest represents 75 million+ U.S. patients and half of U.S. physicians and hospitals. Quest's data includes lab tests, test results, and often diagnoses. Tests range from blood panels to esoteric tests for oncology or rare disease screening.

Appendix 2. Creation of linked, de-identified dataset

To create linkages across data sources and ensure de-identified patient data, HealthVerity Identity Manager was used to de-identify patient records behind the data owner's firewall and assign a universal patient identifier. Using probabilistic matching, HealthVerity matched patient identities to a continuously updated referential database and leveraged machine learning techniques to ensure the highest accuracy rate when assigning an identifier. An independent third-party reviewer ensured Health Insurance Portability and Accountability Act (HIPAA) compliance via Expert Determination. The final linked data set accessed by the research team did not contain protected health information or personal identifying information.

Appendix 3. Limitation of eligibility criteria for patients aged ≥ 2 and < 9 years

It is recommended that children less than 9 years of age who have not been previously vaccinated against influenza should receive two doses at least 4 weeks apart. As such, eligibility criteria for patients aged <2 years specifies that in addition to a record of receiving the QIVc or QIVe vaccination during the Vaccination Intake Timeframe (August 1, 2023 to May 4, 2024), patient had one of the following:

- One homologous QIVc or QIVe vaccine administration at least 28 days following the first administration (identified in Step 1) and within the Vaccination Intake Timeframe OR
- A record of at least one influenza vaccine administration between August 1, 2022 and May 20, 2023 (end of the prior influenza season)

Since the dataset was only licensed from 1 June in the preceding season (i.e., June 1, 2022), it was not possible to confirm the receipt of a previous influenza vaccine in patients aged 2 years and older. This is a limitation of the analysis.

Appendix 4. Outcome definitions, identifying relevant test results and mapping unstructured data to identify positive versus negative results

Outcomes were defined based on a patient's influenza test results within the season timeframe. Influenza test results were classified as 'Negative/Not Detected' or 'Positive/Detected.' A case was defined by a positive influenza test result within the season timeframe ascertained using CPT or LOINC codes (**Supplementary Table 3**) and unstructured text in the test result name field test found in the EHR and laboratory data sources. Influenza test results were reported in both structured and unstructured forms in the data. Structured results refer to a SNOMED concept. Unstructured, or non-standardized, results are short phrases sent from the lab or entered in the EHR to describe the result.

Relevant influenza test results were identified in unstructured text in the test result name field, using the following process:

1. Find all records with "flu" in the result name OR with one of our LOINC/CPT codes indicating molecular/antigen flu tests (case insensitive).
2. Exclude records with any of the following strings in the result name (case-insensitive): 'cov', 'rsv', 'para', 'haemo', 'fluid', 'sars', 'fluo', 'you', 'fluaz', 'flun', 'flur', 'flux', 'symptom', 'cult', 'antib', 'influenzae', 'flubr', 'flualp', 'fluph', 'fluvox'.
3. Exclude records with any of the following strings in the test name (case insensitive): 'influenzae', 'culture', 'igm', 'cmv igm' (any occurrence of 'cmv' prior to 'igm', does not have to exactly be 'cmv igm').
4. Exclude records with the following string in the qualitative result field (case insensitive): 'covid'.
5. Exclude records identified through text string search that contain a LOINC or CPT code not listed in **Supplementary Table 3**, (e.g., a LOINC for an antibody or culture test result).
    a. The following codes were considered allowable even though they are not in **Supplementary Table 3**, as long as the corresponding record qualified for inclusion via text string search: 95941-1, 92882-0, 100345-8, 3185, and 3190. The LOINC codes 95941-1, 92882-0, and 100345-8 represent panels that

include tests for other respiratory infections in addition to influenza. With a panel LOINC code alone, it was unclear whether a positive or negative result was referring to influenza or to another respiratory infection. However, if accompanied by a test result name that qualifies for inclusion via text string search, the test result name clearly indicated that the result was for influenza specifically. Codes 3185 and 3190 are not known LOINC codes, so there was no reason to exclude records containing these codes.

Test result values are reported in unstructured form. Unstructured, or non-standardized, results are short phrases sent from the lab or entered in the EHR to describe the result. The unstructured data is mapped to categories of 'Negative/Not Detected' and 'Positive/Detected' for the purposes of this analysis using the following process:

1. First, entries that have both the terms 'pos' and 'neg' or both symbols '-' and '+' in them are mapped these to 'Positive and Negative.' For the purposes of these analyses, these terms will be considered Positive findings, as at least one flu type was marked to be positive.
2. Next, remaining entries that have either the term 'neg' or 'not detect' or the symbol '-' are mapped to 'Negative/Not Detected'.
3. Then, remaining entries that have either the term 'pos' or 'detect' or the symbol '+' are mapped to 'Positive/Detected'.
4. Finally, the remaining entries are categorized as unmapped and cannot be used for analysis.

Within the Health Verity Linked Dataset, multiple dates and data element fields may have been associated with a lab test or result as available. For labs identified in the EHR, the Test Index Date was assigned using the first populated field in the following order of priority: Lab Result Date, Lab Test Executed Date, Lab Test Sample Collection Date, Encounter Date, Lab Test, Scheduled Date, Lab Order Date, Data Capture Date. For labs identified in Quest or LabCorp data, the Test Index Date was set as the Service Date. If the Service Date field did not populate, the Specimen Date was used alternatively.

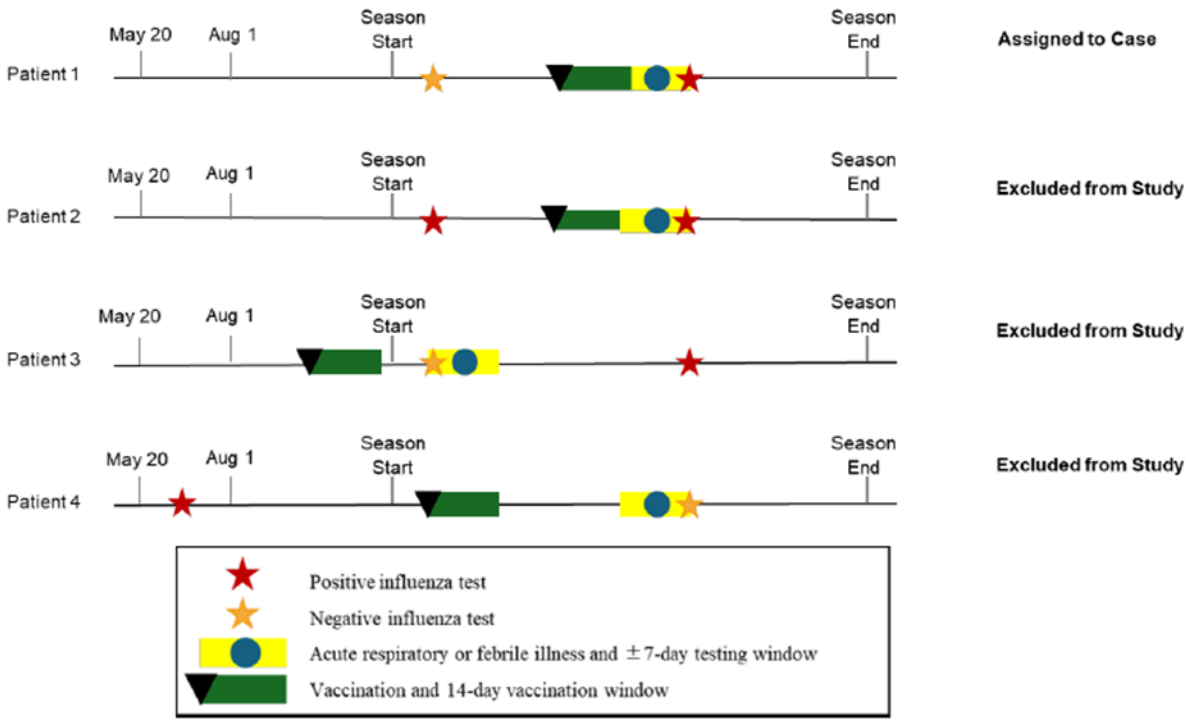
If a patient had multiple influenza test results in a given season, the following logic was implemented to select the relevant test result:

- If the patient had both positive and negative test results in a season, the only or earliest positive influenza test result was evaluated. If the evaluated positive test met other test-related criteria*, the patient was assigned as a case. If the patient did not meet the criteria, they were excluded.

    - * To meet all test-related criteria, a test was required to be within +/-7 days of a documented ARFI during the influenza season and at least 14 days following vaccination. Additionally, patients with positive test results prior to the beginning of the season were excluded.
- Else if the patient had no negative influenza test results and more than one positive influenza test result in a season, the earliest positive influenza test result was evaluated. If the evaluated positive test met other test-related criteria, the patient was assigned as a case. If the patient did not meet the criteria, they were excluded.
- Else if the patient had no positive influenza test results and more than one negative result in a season, the earliest negative influenza test was evaluated. If the evaluated negative test meets other test-related criteria, the patient was assigned as a control. If the patient did not meet the criteria, they were excluded.

Hence, within a given season, each patient was assigned one status, either case or control, and controls will have to have been tested negative through the end of the influenza season (i.e., have no positive results). This logic is consistent with the principle of cumulative seasonal incidence. The figure below shows four synthetic patient event histories as examples to help illustrate how case assignment was performed. Patient 1 would be assigned to the case population because they had an ARFI during the influenza season within +/- 7 days of their first positive influenza test and at least 14 days after their vaccination. The prior influenza test does not impact case assignment because it was a negative test. Patient 2 would be excluded from the study because their first positive test came before their vaccination. Patient 3 would be excluded from the study because their first positive test was not within +/- 7 days of an ARFI. The earlier negative test would not be evaluated because the patient had a positive test during the season. Patient 4 would be excluded from the study because they had a positive influenza test prior to the beginning of the season.

Figure: Case assignment and exclusion examples.



Molecular tests (e.g., PCR and other high-sensitivity testing methods) and antigen tests were included, and the type of test was recorded as a covariate to enable consideration of subgroup analysis by test type if feasible. We endeavored to exclude antibody tests (to avoid potential bias due to the lack of specificity to reliably detect acute disease) and culture tests (due to potential differences in patients tested by culture methods). However, there were many cases with an unknown test type, so we cannot guarantee that all antibody and culture tests were excluded.

Appendix 5. Statistical analysis

The following variables were captured at the Vaccination Date, at the Test Index Date, during the 6 months prior to the Test Index Date, or during the Pre-Vaccination Periods for patients included in this study:

- Captured at Vaccination Date:
    - Source of vaccination data (EHR, claims, both); for descriptive analysis only.
    - Age at Date of Vaccination (continuous, categorical: 6 months–4 year, 5–17, 18–49, 50–64 years). Defined as spline function in adjusted analysis.
    - Week of vaccination date (number of weeks since the start of the Vaccination Intake Time Frame).
- Captured at Test Index Date:

- Source of test result data (EHR, laboratory, both); for descriptive analysis only.
- Sex (Female, Male).
- Race (Asian, Black or African American, White, Other, Not Reported); Race, only available from the Inovalon Closed Claims data source, is a self-reported data field and was limited to the descriptive analysis.
    - Race was limited to the descriptive analysis because the data element was only available from the Inovalon Closed Claims data source, as a self-reported data field. A feasibility analysis indicated that more than 60% of patients had unknown race.
- Ethnicity (Hispanic, Not Reported); for descriptive analysis only; A feasibility analysis indicated that 15% of patients identified as Hispanic. For the remaining patients, the Hispanic ethnicity indicator was not present. However, there was no way to determine whether the patient was non-Hispanic or missing ethnicity information; ethnicity was limited to the descriptive analysis.
- Payer (Commercial, Medicaid, Medicare, Unknown/Other).
- Geographic region (Region 1–Region 10), categorized according to the definition from the U.S Department of Health and Human Services (HHS).
    - HHS Region 1 (Boston): Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, Vermont.
    - HHS Region 2 (New York): New Jersey, New York, Puerto Rico, and the Virgin Islands.
    - HHS Region 3 (Philadelphia): Delaware, District of Columbia, Maryland, Pennsylvania, Virginia, West Virginia.
    - HHS Region 4 (Atlanta): Alabama, Florida, Georgia, Kentucky, Mississippi, North Carolina, South Carolina, Tennessee.
    - HHS Region 5 (Chicago): Illinois, Indiana, Michigan, Minnesota, Ohio, Wisconsin.
    - HHS Region 6 (Dallas): Arkansas, Louisiana, New Mexico, Oklahoma, Texas.
    - HHS Region 7 (Kansas City): Iowa, Kansas, Missouri, Nebraska.
    - HHS Region 8 (Denver): Colorado, Montana, North Dakota, South Dakota, Utah, Wyoming.

        - HHS Region 9 (San Francisco): Arizona, California, Hawaii, Nevada, American Samoa, Commonwealth of the Northern Mariana Islands, Federated States of Micronesia, Guam, Marshall Islands, Republic of Palau.
        - HHS Region 10 (Seattle): Alaska, Idaho, Oregon, Washington.
    - Test Index Date (calendar days since the start of the influenza season). In descriptive tables, shown as month of Index Date and graphed as number of weeks since the start of the influenza season. Defined as a spline function in adjusted analysis.
    - Time to/from ARFI diagnosis from/to Test Index Date (continuous, -7 to +7 days); limited to descriptive analysis only.
    - Test type (antigen, molecular, unknown).
    - Influenza type/subtype (A, A(H1N1), A(H3N2) B, not available) among cases; limited to descriptive analysis only and for identifying patients for exploratory subgroup analysis.
    - Outpatient test setting (yes, no); limited to descriptive analysis only and for identifying patients for exploratory subgroup analysis.
        - All lab results from Labcorp, Question Diagnostics, Veradigm EHR, and Source 42 EHR sources were from the outpatient setting. However, Inovalon EMR labs could have been from the inpatient or outpatient setting. Because there is no indicator of setting in the Inovalon EMR records, we were only able to identify setting for patients with a lab result from Inovalon EMR if the dataset contained a claim for the patient from the same date.
- Captured during the 6 months prior to Test Index Date:
    - COVID-19 Vaccination Receipt within the past 6 months (yes/no).
        - Administrative codes for each vaccine in **Supplementary Table 4**.
    - Captured during the Pre-Vaccination Period (up to 12 months as available).
    - Charlson Comorbidity Index (CCI) [12].
    - Presence of underlying conditions identified by the CDC [13, 14] as posing a higher risk of complications due to influenza (yes/no) (**Supplementary Table 7**).
    - Presence of at least one high-risk condition (yes/no); limited to descriptive analysis only.

    - Number of underlying conditions (categorical: 0, 1, 2, 3+).
- **Captured during the Pre-Vaccination Period (6 months prior to vaccination)**:
    - Healthcare resource utilization defined by three variables:*
        - Number of outpatient visits (all-cause) (categorical: unknown, 0, 1+).
        - Number of inpatient admissions (all-cause) (categorical: unknown, 0, 1+).
        - Number of emergency room visits (all-cause) (categorical: unknown, 0, 1+).
        - Inpatient and emergency room visits were determined from claims only. Outpatient visits were determined from claims and EHR sources other than Inovalon EMR. (Inovalon EMR does not indicate setting. All other EMR sources are outpatient only). Approximately three-fourths of patients had at least one claim in the 6 months prior to vaccination, and approximately one-third had continuous enrollment in claims for the 6 months prior to vaccination. For inpatient and emergency room visits, patients without claims activity but with continuous enrollment were assumed to have zero inpatient and emergency encounters during the baseline period. Patients without claims activity and without continuous enrollment were categorized as having "unknown" inpatient and emergency utilization. For outpatient visits, patients without an EHR outpatient visit and without claims activity but with continuous enrollment were assumed to have zero outpatient encounters during the baseline period. Patients without an EHR outpatient visit, without claims activity, and without continuous enrollment were categorized as having "unknown" outpatient utilization.

Descriptive analysis

Summary tables of patient baseline demographic and clinical characteristics are reported by vaccine type (QIVc, QIVe), by case status (influenza test positive versus influenza test negative), and by both case status and vaccine type (cases with QIVc, controls with QIVc, cases with QIVe, controls with QIVe). Categorical variables are presented as counts and percentages, continuous variables were presented by mean, standard deviation, median, and interquartile range. The proportion of patients with missing or unknown, or undocumented

values for sex, race, and ethnicity are also reported. The percentage of patients with Test Index Dates in each week of the influenza season is summarized by vaccine type and by case status in descriptive tables and presented as figures. The proportion of tests by influenza type and subtype, and the number of tests specific to outpatient setting is also summarized. These descriptive results were used to determine feasibility of influenza type-specific and outpatient setting-specific analyses. Vaccine exposure group balance for covariates among the controls and differences between cases and controls were assessed using Austin's standardized mean difference (SMD) [13].

Covariate Balance – Standardized Mean Differences

In a test-negative design study, the test-negative group is intended to represent the vaccination distribution in the overall source-eligible population (i.e., the population vaccinated with QIVc or QIVe). It is within this control group that characteristics of patients in each vaccine group are evaluated for potential confounding [15]. For this study, covariate balance between vaccine exposure groups among the controls were assessed using SMDs. An SMD with an absolute value ≤ 0.1 was used to indicate a negligible difference in proportions between the groups [13]. SMDs were generated to assess differences in each variable between the QIVc and QIVe controls prior to any statistical adjustment or modification. The following variables were included in the inverse probability of treatment weighting (IPTW) if determined to be imbalanced based on SMD: week of vaccination, test type, payer, mean CCI, each individual high-risk condition flag, mean number of high-risk conditions, number of outpatient (OP) visits (categorical), number of inpatient (IP) admissions (categorical), and number of ER visits (categorical).

The standardized difference compares the difference in means in units of the pooled standard deviation. Unlike other statistical tests of hypothesis, the SMD is not influenced by sample size. Thus, the use of the SMD can be used to compare balance in measured variables among the QIVc- and QIVe-exposed controls in the unweighted sample with balance in a weighted sample.

For continuous variables, the SMD is defined as:

$$d = \frac{(\bar{x}_{group\ 1} - \bar{x}_{group\ 0})}{\sqrt{\frac{s^2_{group\ 1} + s^2_{group\ 0}}{2}}}$$

where $\bar{x}_{group\ 1}$ and $\bar{x}_{group\ 0}$ denote the sample means of the covariate in the QIVc and QIVe exposure groups among controls (or case and control group for the univariate comparison), while $s^2_{group\ 1}$ and $s^2_{group\ 0}$ denote the sample variances of the covariate in the QIVc and QIVe group (or case and control group).

For categorical variables, the SMD is defined as:

$$d = \frac{(\hat{p}_{group\ 1} - \hat{p}_{group\ 0})}{\sqrt{\frac{\hat{p}_{group\ 1}(1 - \hat{p}_{group\ 1}) + \hat{p}_{group\ 0}(1 - \hat{p}_{group\ 0})}{2}}}$$

where $\hat{p}_{group\ 1}$ and $\hat{p}_{group\ 0}$ denote the prevalence or means of the categorical variable in the QIVc and QIVe exposure group among the controls (or case and control group).

Primary analyses

The relative vaccine effectiveness between QIVc and QIVe was assessed using a retrospective test-negative design. With this design, the same criteria is used for selection of both cases and controls, minimizing the likelihood for selection bias in observational studies [16, 17]. This principle was applied in the current study by restricting to vaccinated subjects with a record of a ARFI within 7 days (before or after) of the influenza test during the influenza season. The rVE compared the odds of testing positive for influenza among QIVc vs. QIVe recipients. A generalized linear model with a logit link was used to obtain ORs comparing influenza-positive cases and influenza-negative controls, with vaccine type received as the exposure of interest. The primary analysis used a doubly robust approach that combines IPTW and multivariable adjustment. The adjusted rVE were calculated using the formula rVE = $(1 - OR_{Adjusted}) \times 100$ and reported with 95% confidence intervals. Unadjusted ORs and 95% CI are also reported.

Covariate Transformation

The primary analysis adjusted for calendar time (in days) between the start of the influenza season and the Test Index Date to capture variation in the risk of infection over time and potential waning of vaccine effectiveness as the season progressed. Because it was assumed that the confounding effects of time on vaccination and influenza test result were not linear, the variable for time from start of the influenza season to Test Index Date was transformed

using a spline function to summarize the non-linear relationship between elapsed time and influenza test result [18]. The approach used a restricted cubic spline to split the range of values of elapsed time into intervals using 'knots' that define where one interval ends, and another begins. Prior to inclusion in the adjusted analysis, the optimal number (e.g., 3, 4, or 5) and placement (e.g., at quartiles, quintiles, etc.) of knots was determined using a combination of the following methods: visual presentation of the spline models, Bayesian Information Criterion (BIC) [19], and Akaike information criteria (AIC) [20].

The age covariate also underwent transformation into a spline variable to better capture its non-linear influence on the risk of infection and vaccine effectiveness. Knot placements were assessed using either a data driven approach (similar to the approach which was used for calendar time (in days)), or an *a priori* hypothesis aligned with key age groups for vaccine recommendations, specifically 5, 18, and 50 years. The spline models with varying number of knots (e.g., 1, 2 or 3) and placements were fitted, and the optimal number and placement of knots was determined using a combination of the following methods: visual presentation of the spline models, BIC, and AIC.

Weighting Using Inverse Probability Treatment Weighting

Stabilized IPTWs were used to account for the *a priori*-defined covariates age (as spline), sex, region, Test Index Date (as spline), COVID-19 vaccination history, and any additional covariate with an SMD with an absolute value >0.1. IPTW allowed maximal use of available data but may be distorted by cases with very large or very small propensity scores, which may result in very small or large IPTW values. Stabilized weighting avoids the effect of extreme weights on the variability of the estimated treatment effect.

The methodology used to perform stabilized IPTW was as follows:

1. Among the influenza-negative controls, logistic regression models predictive of treatment group membership (i.e., QIVc vs. QIVe) provided propensity scores pj based on the study covariates listed in **Supplementary Table 5**. The models included the *a priori* covariates and additional covariates identified as having a non-negligible difference (imbalanced) between vaccine groups among the controls.
2. These fitted models were then applied to the influenza-positive cases to calculate propensity of treatment group membership scores for the cases (pj).
3. Next, both cases and controls in each of the vaccine groups were assigned a stabilized weight as follows:

a. IPTW values wj are calculated as wj = 1 / (pj) for the QIVc group and wj = 1 / (1-pj) for the QIVe group.
b. Stabilized weights w*j were obtained by multiplying IPTW values by the proportion of individuals in the QIVc and QIVe groups, respectively. For the QIVc group w*j = pt * wj, while for the QIVe group w*j = (1- pt) * wj where pt = Nt / (Nt+Nc), the proportion of individuals in the QIVc group. Nt is the number of patients in the QIVc group, and Nc is the number of patients in the QIVe group.

4. An absolute standardized difference value was calculated for all covariates (categorical as well as continuous variables). The absolute standardized difference compares the difference in means of covariates measured in standard deviation units.
5. To mitigate the impact of outliers, the stabilized weights were winsorized (i.e., weights that exceeded prespecified thresholds of 1st and 99th percentiles were set to that threshold [21].

Primary Analysis (Doubly Robust)

The primary analysis used a doubly robust approach to adjust for any potential confounding [22]. The IPTW sample was used in a multivariable model with age (as spline), sex, region, Test Index Date (as spline), COVID-19 vaccination history, and any other covariates that remained imbalanced following IPTW.

Estimate π=Pr(influenza positive=1|x) for logit(π)= $\alpha + \beta'x$ where each observation is appropriately IPTW weighted and x is a multi-item vector of vaccine type (QIVc vs. QIVe), *a priori*-defined covariates and remaining imbalanced study covariates

Secondary analyses (Subgroups)

Four subgroup analyses were conducted. As these analyses were all powered at >99% to detect the 19.8 rVE estimated for the full study population, they were considered secondary rather than exploratory. The first subgroup analysis limited to patients tested in the outpatient setting. The second subgroup analysis limited cases to patients who tested positive for influenza A only. Age subgroups included patients aged 0–17 years (pediatric) and 18–64 years (adults).

For the outpatient only and influenza A analyses, we applied the doubly robust methodology that was used in the main analysis, including reweighting of the IPTWs based on the subgroup of interest.

For the age subgroup analyses, we conducted the analysis in two stages. First, as a model-building step, we analyzed the full population by fitting two models: one with the addition of an age group variable and another with both the age group variable and an interaction term between age group and treatment. The statistical significance of incorporating the interaction term was determined by comparing these two models using the likelihood ratio test. Second, we ran separate models for the two age groups (patients aged 0–17 years and patients aged 18–64 years), applying the same doubly robust adjustment. More specifically, for each age group, we assessed covariate balance and perform IPTW including the five *a priori*-defined covariates age (as spline), sex, region, Test Index Date (as spline) and COVID vaccination history as well as any other covariates that were imbalanced within the age group. After weighting, the multivariable logistic regression was conducted, adjusting for the same five *a priori* covariates and any other covariates that remained imbalanced within the age group following the IPTW. Note that the age (as spline) and Test Index Date (as spline) covariates were refitted based on the specific age group of interest.

Missing Values

Among demographic variables, missing values were captured as a category—i.e., as "Missing" or "Not Reported". Patients with missing values for region or sex were excluded from the study. For the continuous variables CCI, an absence of a score was coded to 0, signifying that the patient did not have any of the conditions used for the CCI.

Sensitivity analyses

Two prespecified sensitivity analyses were conducted to evaluate the robustness of key assumptions and residual confounding in the main analysis.

1. Propensity to be tested

This sensitivity analysis addressed the potential bias of which patients are given an influenza test. The analysis assessed all vaccinated (with QIVc or QIVe) patients with a documented ARFI during the influenza season, for whom we calculated the propensity to be tested during the influenza season. Demographic (age, sex, and region) and clinical (CCI score, COVID vaccination history, high-risk conditions, and week of vaccination) covariates were used to

estimate the propensity to be tested, and propensity-for-testing estimators were created using the inverse of the score. Healthcare utilization and payer covariates were not included due to convergence and/or missing data issues. The main analysis was then repeated, additionally accounting for propensity-for-testing scores as a covariate in the model.

2. Exact matching on week of Test Index Date

In this sensitivity analysis, rather than adjusting for time from influenza season start date to Test Index Date (as spline), cases were matched with up to five controls on the exact week of the Test Index Date (test week). The intent was to further examine if there was confounding associated with the timing of the test via a matched analysis, which was less sensitive to model misspecification [23, 24]. A greedy nearest neighbor approach was used to match cases to controls by test week only. After matching on calendar week, doubly robust IPTW and multivariable conditional logistic regression methodology was applied (although other analyses did not use conditional logistic regression, we used it for this sensitivity analysis because of the inclusion of matched data). We stratified the analysis by matched risk set. The model excluded the spline function for the Test Index Date.

Supplementary Appendix 6. Administrative codes used to identify high-risk conditions

In separate Excel spreadsheet.

Supplementary Appendix 7. Influenza B confirmatory analyses

- Matched on Test Index Date

A *post-hoc* subgroup analysis limited cases to patients with influenza B and matched cases and controls based on Week of Test Index Date was conducted. The population for this analysis comprised of 26,262 patients, which represented 19% of the full study population. Among patients in this analysis, 15% received a QIVc vaccine (*n* = 3960) and 85% received a QIVe vaccine (*n* = 22,302). All cases were matched to five controls each. As such, 17% of the analysis population were cases (*n* = 4377) and 83% (*n* = 21,885) were controls.

Table: Influenza B Matched Analysis Population as Proportion of Full Study Population

	Total	**Vaccine**		**Case Status**	
		QIVc	**QIVe**	**Cases**	**Controls**
Number	26,262	3960	22,302	4377	21,885
% of Subgroup Total	100%	15%	85%	17%	83%
% of Full Study Population	25%	23%	25%	26%	24%

QIVc, cell-based quadrivalent influenza vaccine; QIVe, egg-based quadrivalent influenza vaccine.

Among the influenza B matched analysis population, more than half of patients had Test Index Dates in February (31%) or March (24%). Mean week of vaccination was 12.7 weeks from the start of the season. The mean (SD) age was 22.5 (21.1) years old among all patients included in the analysis, 28.5 (22.1) years among QIVc recipients, and 21.4 (20.7) among QIVe recipients. Cases were on average younger than controls (15.8 vs. 23.8 years). Other vaccination and testing, demographic, and clinical characteristics followed similar patterns to those observed in the full study population.

In this post-hoc influenza B matched analysis population, prior to weighting, there was an imbalance (|SMD| >0.1) between the QIVc controls and QIVe controls for several variables. Compared to QIVe controls, QIVc controls were older, vaccinated earlier, had more high-risk conditions, and had a higher CCI score. QIVc controls were also more likely to have a molecular influenza test, to have received a COVID-19 vaccine within the 6 months prior to their influenza test, and to have commercial insurance. QIVe controls were more likely to have an antigen influenza test and unknown insurance. Differences were also observed in regional distribution and prior healthcare resource utilization.

After weighting, all covariates were balanced between QIVc controls and QIVe controls.

- Pediatric population.

Another *post-hoc* subgroup analysis was focused on the pediatric population and limited cases to patients with influenza B. The population for the pediatric influenza B analysis comprised of 52,893 patients, which represented 50% of the full study population. Among patients in this analysis, 12% received a QIVc vaccine (*n* = 6292) and 88% received a QIVe vaccine (*n* = 46,601). In terms of case status, 6% of the analysis population were cases (*n* = 3342) and 94% were controls (*n* = 49,551).

Table: Pediatric Influenza B Analysis Population as Proportion of Full Pediatric Population and Full Study Population

	Total	**Vaccine**		**Case Status**	
		QIVc	**QIVe**	**Cases**	**Controls**
Number	52,893	6292	46,601	3342	49,551
% of Subgroup Total	100%	12%	88%	6%	94%
% of Pediatric Population	87%	87%	87%	29%	100%

% of Full Study Population	50%	37%	52%	20%	55%

QIVc, cell-based quadrivalent influenza vaccine; QIVe, egg-based quadrivalent influenza vaccine.

Generally, trends in vaccination and testing characteristics, demographic characteristics, and clinical characteristics of the pediatric influenza B analysis population followed a similar pattern to those of the full pediatric population.

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