Supplemental Information for Effectiveness of BNT162b2 XBB vaccine in the US Veterans Affairs Healthcare System

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Supplemental Table 1. Acute respiratory infection diagnosis codes (ICD-10)

ICD-10 Code	Diagnosis
A22.1	Pulmonary anthrax
A37.00	Whooping cough due to *Bordetella pertussis* without pneumonia
A37.01	Whooping cough due to *Bordetella pertussis* with pneumonia
A37.10	Whooping cough due to *Bordetella parapertussis* without pneumonia
A37.11	Whooping cough due to *Bordetella parapertussis* with pneumonia
A37.80	Whooping cough due to other Bordetella species without pneumonia
A37.81	Whooping cough due to other Bordetella species with pneumonia
A37.90	Whooping cough, unspecified species without pneumonia
A37.91	Whooping cough, unspecified species with pneumonia
A48.1	Legionnaires' disease
B25.0	Cytomegaloviral pneumonitis
B34.2	Coronavirus infection, unspecified
B44.0	Invasive pulmonary aspergillosis
B77.81	Ascariasis pneumonia
B97.29	Other coronavirus as the cause of diseases classified elsewhere
J00*	Acute nasopharyngitis [common cold]
J01*	Acute sinusitis
J02*	Acute pharyngitis
J03*	Acute tonsillitis
J04*	Acute laryngitis and tracheitis
J05*	Acute obstructive laryngitis [croup] and epiglottitis
J06*	Acute upper respiratory infections of multiple and unspecified sites
J09.X1	Influenza due to novel influenza a virus with pneumonia
J09.X2	Influenza due to identified novel influenza A virus with other respiratory manifestations
J09.X3	Influenza due to identified novel influenza A virus with gastrointestinal manifestations
J09.X9	Influenza due to identified novel influenza A virus with other manifestations
J10.00	Influenza due to other identified influenza virus with pneumonia
J10.01	Influenza due to other identified influenza virus with the same other identified influenza virus pneumonia
J10.08	Influenza due to other identified influenza virus with other specified pneumonia
J10.1	Influenza due to other identified influenza virus with other respiratory manifestations
J10.2	Influenza due to other identified influenza virus with gastrointestinal manifestations
J10.8*	Influenza due to other identified influenza virus with other manifestations
J10.81	Influenza due to other identified influenza virus with encephalopathy
J10.82	Influenza due to other identified influenza virus with myocarditis
J10.83	Influenza due to other identified influenza virus with otitis media
J10.89	Influenza due to other identified influenza virus with other manifestations
J11.00	Influenza due to unidentified influenza virus with pneumonia
J11.08	Influenza due to unidentified influenza virus with specified pneumonia
J11.1	Influenza due to unidentified influenza virus with other respiratory manifestations
J11.2	Influenza due to unidentified influenza virus with gastrointestinal manifestations
J11.81	Influenza due to unidentified influenza virus with encephalopathy
J11.82	Influenza due to unidentified influenza virus with myocarditis
J11.83	Influenza due to unidentified influenza virus with otitis media
J11.89	Influenza due to unidentified influenza virus with other manifestations
J12.0	Adenoviral pneumonia
J12.1	Respiratory syncytial virus pneumonia
J12.2	Parainfluenza virus pneumonia
J12.3	Human metapneumovirus pneumonia
J12.81	Pneumonia due to SARS-associated coronavirus
J12.82	Pneumonia due to coronavirus disease 2019
J12.89	Other viral pneumonia
J12.9	Viral pneumonia, unspecified
J13	Pneumonia due to *Streptococcus pneumoniae*
J14	Pneumonia due to *Hemophilus influenzae*

ICD-10 Code	Diagnosis
J15.0	Pneumonia due to *Klebsiella pneumoniae*
J15.1	Pneumonia due to Pseudomonas
J15.20	Pneumonia due to Staphylococcus, unspecified
J15.211	Pneumonia due to methicillin susceptible *Staphylococcus aureus*
J15.212	Pneumonia due to methicillin resistant *Staphylococcus aureus*
J.15.29	Pneumonia due to other Staphylococcus
J15.3	Pneumonia due to Streptococcus, group b
J15.4	Pneumonia due to other Streptococci
J15.5	Pneumonia due to *Escherichia coli*
J15.6	Pneumonia due to other aerobic gram-negative bacteria
J15.7	Pneumonia due to *Mycoplasma pneumoniae*
J15.8	Pneumonia due to other specified bacteria
J15.9	Unspecified bacterial pneumonia
J16.0	Chlamydial pneumonia
J16.8	Pneumonia due to other specified infectious organisms
J17	Pneumonia in diseases classified elsewhere
J18.0	Bronchopneumonia, unspecified organism
J18.1	Lobar pneumonia, unspecified organism
J18.2	Hypostatic pneumonia, unspecified organism
J18.8	Other pneumonia, unspecified organism
J18.9	Pneumonia, unspecified organism
J20.0	Acute bronchitis due to *Mycoplasma pneumoniae*
J20.1	Acute bronchitis due to *Hemophilus influenzae*
J20.2	Acute bronchitis due to Streptococcus
J20.3	Acute bronchitis due to coxsackievirus
J20.4	Acute bronchitis due to parainfluenza virus
J20.5	Acute bronchitis due to respiratory syncytial virus
J20.6	Acute bronchitis due to rhinovirus
J20.7	Acute bronchitis due to echovirus
J20.8	Acute bronchitis due to other specified organisms
J20.9	Acute bronchitis, unspecified
J21.*	Acute bronchiolitis
J21.0	Acute bronchiolitis due to respiratory syncytial virus
J21.1	Acute bronchiolitis due to human metapneumovirus
J21.8	Acute bronchiolitis due to other specified organisms
J21.9	Acute bronchiolitis, unspecified
J22	Unspecified acute lower respiratory infection
J80	Acute respiratory distress syndrome
J96.00	Acute respiratory failure unspecified whether with hypoxia or hypercapnia
J96.01	Acute respiratory failure with hypoxia
J96.02	Acute respiratory failure with hypercapnia
J96.10	Chronic respiratory failure, unspecified with hypoxia or hypercapnia
J96.11	Chronic respiratory failure with hypoxia
J96.12	Chronic respiratory failure with hypercapnia
J96.20	Acute and chr resp failure, unspecified with hypoxia or hypercapnia
J96.21	Acute and chronic respiratory failure with hypoxia
J96.22	Acute and chronic respiratory failure with hypercapnia
J96.90	Respiratory failure, unspecified, unspecified with hypoxia or hypercapnia
J96.91	Respiratory failure, unspecified with hypoxia
J96.92	Respiratory failure, unspecified with hypercapnia
M35.81	Multisystem inflammatory syndrome
R04.2	Hemoptysis
R05	Cough
R05.1	Acute cough
R05.2	Subacute cough
R05.3	Chronic cough
R05.4	Cough syncope

ICD-10 Code	Diagnosis
R05.8	Other specified cough
R05.9	Cough, unspecified
R06.00	Dyspnea/abnormalities of breathing unspecified
R06.02	Shortness of breath
R06.03	Acute respiratory distress
R06.09	Other forms of dyspnea
R06.1	Stridor
R06.82	Tachypnea, not elsewhere classified
R06.89	Other abnormalities of breathing
R07.1	Chest pain on breathing
R09.0*	Asphyxia and hypoxemia
R09.01	Asphyxia
R09.02	Hypoxemia
R09.1	Pleurisy
R09.2	Respiratory arrest
R50.9	Fever, unspecified
U04*	SARS (WHO 2019)
u04.9	SARS, unspecified (WHO 2019)
U07.1	COVID-19
U07.2	COVID-19, virus not identified (clinically diagnosed)

Supplemental Table 2. Medical history of acute respiratory infection episodes (hospitalization, ED/UC visits, outpatient visits) with SARS-CoV-2 testing, by COVID-19 case-control status

	Total (n=113,174)	**Test-positive COVID-19 cases (n=20,523)**	**Test-negative controls (n=92,651)**	***P*-value**
Medical History Acute cerebrovascular disease	5,372 (4.7)	907 (4.4)	4,465 (4.8)	0.015
Acute myocardial infarction	3,842 (3.4)	533 (2.6)	3,309 (3.6)	<0.001
Alcohol and substance related disorders	28,011 (24.8)	4,657 (22.7)	23,354 (25.2)	<0.001
Any cancer or malignancy	42,527 (37.6)	7,452 (36.3)	35,075 (37.9)	<0.001
Aortic and peripheral arterial embolism or thrombosis	440 (0.4)	51 (0.2)	389 (0.4)	<0.001
Asthma	10,024 (8.9)	1,516 (7.4)	8,508 (9.2)	<0.001
Benign prostatic hyperplasia	23,037 (20.4)	3,930 (19.1)	19,107 (20.6)	<0.001
Cardiac dysrhythmias	27,478 (24.3)	4,439 (21.6)	23,039 (24.9)	<0.001
Chronic kidney disease	13,161 (11.6)	2,165 (10.5)	10,996 (11.9)	<0.001
Chronic obstructive pulmonary disease and bronchiectasis	26,259 (23.2)	3,381 (16.5)	22,878 (24.7)	<0.001
Congestive heart failure	17,429 (15.4)	2,343 (11.4)	15,086 (16.3)	<0.001

	Total (n=113,174)	**Test-positive COVID-19 cases (n=20,523)**	**Test-negative controls (n=92,651)**	***P*-value**
Coronary atherosclerosis and other heart disease	25,404 (22.4)	4,098 (20.0)	21,306 (23.0)	<0.001
Delirium, dementia, and other cognitive disorders	9,559 (8.4)	1,684 (8.2)	7,875 (8.5)	0.170
Diabetes with or without chronic complications	47,147 (41.7)	8,376 (40.8)	38,771 (41.8)	0.007
Epilepsy	3,142 (2.8)	525 (2.6)	2,617 (2.8)	0.036
Human immunodeficiency virus (HIV) infection	1,271 (1.1)	181 (0.9)	1,090 (1.2)	<0.001
Hypertension	66,411 (58.7)	11,722 (57.1)	54,689 (59.0)	<0.001
Influenza	1,413 (1.2)	262 (1.3)	1,151 (1.2)	0.689
Liver diseases	10,877 (9.6)	1,862 (9.1)	9,015 (9.7)	0.004
Mental health conditions	57,479 (50.8)	10,305 (50.2)	47,174 (50.9)	0.068
Osteoarthritis	23,617 (20.9)	4,320 (21.0)	19,297 (20.8)	0.479
Peripheral and visceral atherosclerosis	9,699 (8.6)	1,547 (7.5)	8,152 (8.8)	<0.001
Pneumonia	9,596 (8.5)	1,156 (5.6)	8,440 (9.1)	<0.001
Pulmonary heart disease	7,598 (6.7)	974 (4.7)	6,624 (7.1)	<0.001

	Total (n=113,174)	**Test-positive COVID-19 cases (n=20,523)**	**Test-negative controls (n=92,651)**	***P*-value**
Rheumatoid arthritis	2,273 (2.0)	367 (1.8)	1,906 (2.1)	0.013
Septicemia	4,805 (4.2)	654 (3.2)	4,151 (4.5)	<0.001
Thyroid disorder	14,098 (12.5)	2,450 (11.9)	11,648 (12.6)	0.013
Tuberculosis	237 (0.2)	31 (0.2)	206 (0.2)	0.043

ARI= acute respiratory infection; ED/UC= emergency department/urgent care; VA= Veterans Affairs

Data are n (%) unless otherwise specified.

All ARI encounters within a 30-day window were considered a single ARI episode. If multiple encounter types occurred during the 30-day window, the highest level of care was used (hospitalization > ED/UC > outpatient).

Medical history included underlying conditions and diagnoses in the year prior to the ARI episode, identified using international classification of diseases (ICD)-10 codes.

Supplemental Table 3. Demographics and clinical characteristics of acute respiratory infection hospitalizations with SARS-CoV-2 testing, by COVID-19 case-control status

	Total (n=24,206)	**Test-positive COVID-19 cases (n=4,561)**	**Test-negative controls (n=19,645)**	***P*-value**
COVID vaccine status*				<0.001
≥1 dose of BNT162b2 XBB vaccine	1,836 (7.6)	257 (5.6)	1,579 (8.0)	
≥1 dose of BA.4/5-adapted bivalent vaccine	7,816 (32.3)	1,443 (31.6)	6,373 (32.4)	0.296
≥3 doses of original wild-type mRNA vaccine but no bivalent-adapted vaccines	6,812 (28.1)	1,263 (27.7)	5,549 (28.2)	0.453
≥2 doses of original wild-type mRNA vaccine but no bivalent-adapted vaccines	10,711 (44.3)	1,966 (43.1)	8,745 (44.5)	0.084
No original wild-type mRNA or bivalent-adapted or non-mRNA vaccines	4,350 (18.0)	912 (20.0)	3,438 (17.5)	<0.001
Time since last non-XBB adapted vaccine, median days (IQR)	595 (392-784)	601 (397-789)	594 (390-783)	0.046
Age group	5,438 (22.5)	1,083 (23.7)	4,355 (22.2)	<0.001

	Total (n=24,206)	**Test-positive COVID-19 cases (n=4,561)**	**Test-negative controls (n=19,645)**	***P*-value**
18–64 years				
65–74 years	7,676 (31.7)	1,289 (28.3)	6,387 (32.5)	
≥75 years	11,092 (45.8)	2,189 (48.0)	8,903 (45.3)	
Sex Male	22,770 (94.1)	4,290 (94.1)	18,480 (94.1)	0.977
Female	1,436 (5.9)	271 (5.9)	1,165 (5.9)	
Body mass index category Underweight (<18.5 kg/m^2)	801 (3.3)	117 (2.6)	684 (3.5)	0.002
Healthy weight (18.5–24.9 kg/m^2)	10,234 (42.3)	2,021 (44.3)	8,213 (41.8)	
Overweight (25–29.9 kg/m^2)	4,338 (17.9)	868 (19.0)	3,470 (17.7)	
Obese (≥30 kg/m^2)	8,801 (36.4)	1,542 (33.8)	7,259 (37.0)	
Missing	32 (0.1)	13 (0.3)	19 (0.1)	
Region Midwest	4,439 (18.3)	980 (21.5)	3,459 (17.6)	<0.001
Northeast	3,113 (12.9)	698 (15.3)	2,415 (12.3)	
West	5,457 (22.5)	1,025 (22.5)	4,432 (22.6)	
South	11,197 (46.3)	1,858 (40.7)	9,339 (47.5)	
Race Black or African American	5,699 (23.5)	1,033 (22.6)	4,666 (23.8)	0.064

	Total (n=24,206)	**Test-positive COVID-19 cases (n=4,561)**	**Test-negative controls (n=19,645)**	***P*-value**
White	16,277 (67.2)	3,073 (67.4)	13,204 (67.2)	
Other race	2,230 (9.2)	455 (10.0)	1,775 (9.0)	
Ethnicity				0.698
Hispanic or Latino	1,768 (7.3)	327 (7.2)	1,441 (7.3)	
Not Hispanic or Latino	22,438 (92.7)	4,234 (92.8)	18,204 (92.7)	
Smoking				<0.001
Current or former	14,803 (61.2)	2,586 (56.7)	12,217 (62.2)	
Never smoked	5,736 (23.7)	1,260 (27.6)	4,476 (22.8)	
Unknown	3,667 (15.1)	715 (15.7)	2,952 (15.0)	
Area deprivation index (ADI)*				0.033
Quintile				
1 (Least Deprived)	4,506 (18.6)	913 (20.0)	3,593 (18.3)	
2	4,398 (18.2)	853 (18.7)	3,545 (18.0)	
3	4,611 (19.1)	868 (19.0)	3,743 (19.1)	
4	4,759 (19.7)	874 (19.2)	3,885 (19.8)	
5 (Most Deprived)	5,284 (21.8)	939 (20.6)	4,345 (22.1)	
Missing	648 (2.7)	114 (2.5)	534 (2.7)	
VA Frailty index (VA-FI)**				0.025
Non-frail (VA-FI $\leq$0.1)	3,557 (14.7)	720 (15.8)	2,837 (14.4)	
Pre-frail (VA-FI >0.1-0.2)	4,679 (19.3)	873 (19.1)	3,806 (19.4)	

	Total (n=24,206)	**Test-positive COVID-19 cases (n=4,561)**	**Test-negative controls (n=19,645)**	***P*-value**
Mildly frail (VA-FI >0.2-0.3)	5,024 (20.8)	989 (21.7)	4,035 (20.5)	
Moderately frail (VA-FI >0.3-0.4)	4,508 (18.6)	815 (17.9)	3,693 (18.8)	
Severely frail (VA-FI ≥0.5)	6,438 (26.6)	1,164 (25.5)	5,274 (26.8)	
Healthcare exposures, 1 year prior				0.180
Hospital admission	12,317 (15.9)	2,280 (50.0)	10,037 (51.1)	
Nursing home admission	1,273 (5.3)	345 (7.6)	928 (4.7)	<0.001
Intensive care unit admission	3,633 (15.0)	631 (13.8)	3,002 (15.3)	0.014
Emergency department visit	17,664 (73.0)	3,254 (71.3)	14,410 (73.4)	0.006
Primary care visit	22,931 (94.7)	4,300 (94.3)	18,631 (94.8)	0.127
Charlson Comorbidity Index				<0.001
0	3,007 (12.4)	733 (16.1)	2,274 (11.6)	
1	3,701 (15.3)	674 (14.8)	3,027 (15.4)	
2	3,179 (13.1)	580 (12.7)	2,599 (13.2)	
3	3,002 (12.4)	560 (12.3)	2,442 (12.4)	
≥ 4	11,317 (46.8)	2,014 (44.2)	9,303 (47.4)	
Immunocompromised***	10,422 (43.1)	1,507 (33.0)	8,915 (45.4)	<0.001
Week of infection	1,161 (4.8)	163 (3.6)	998 (5.1)	<0.001
Sep 25–Sep 30,2023				

	Total (n=24,206)	**Test-positive COVID-19 cases (n=4,561)**	**Test-negative controls (n=19,645)**	***P*-value**
Oct 01–Oct 07, 2023	1,231 (5.1)	186 (4.1)	1,045 (5.3)	
Oct 08–Oct 14, 2023	1,132 (4.7)	176 (3.9)	956 (4.9)	
Oct 15–Oct 21, 2023	1,274 (5.3)	210 (4.6)	1,064 (5.4)	
Oct 22–Oct 28, 2023	1,160 (4.8)	178 (3.9)	982 (5.0)	
Oct 29–Nov 04, 2023	1,053 (4.3)	156 (3.4)	897 (4.6)	
Nov 05–Nov 11, 2023	1,202 (5.0)	195 (4.3)	1,007 (5.1)	
Nov 12–Nov 18, 2023	1,311 (5.4)	261 (5.7)	1,050 (5.3)	
Nov 19–Nov 25, 2023	1,160 (4.8)	241 (5.3)	919 (4.7)	
Nov 26–Dec 02, 2023	1,392 (5.7)	240 (5.3)	1,152 (5.9)	
Dec 03–Dec 09, 2023	1,508 (6.2)	301 (6.6)	1,207 (6.1)	
Dec 10–Dec 16, 2023	1,370 (6.0)	257 (5.6)	1,113 (5.7)	
Dec 17–Dec 23, 2023	1,473 (6.1)	290 (6.4)	1,183 (6.0)	
Dec 24–Dec 30, 2023	1,521 (6.3)	348 (7.6)	1,173 (6.0)	
Dec 31, 2023–Jan 06, 2024	1,693 (7.0)	360 (7.9)	1,333 (6.8)	
Jan 07–Jan 13, 2024	1,537 (6.4)	357 (7.8)	1,180 (6.0)	
Jan 14–Jan 20, 2024	1,225 (5.1)	250 (5.5)	975 (5.0)	
Jan 21–Jan 27, 2024	1,191 (4.9)	272 (6.0)	919 (4.7)	
Jan 28–Jan 31, 2024	612 (2.5)	120 (2.6)	492 (2.5)	
Prior COVID-19 infection****	6,070 (25.1)	880 (19.3)	5,190 (26.4)	<0.001

	Total (n=24,206)	**Test-positive COVID-19 cases (n=4,561)**	**Test-negative controls (n=19,645)**	***P*-value**
ICU admission (hospitalized only)******	4,955 (20.5)	624 (13.7)	4,331 (22.0)	<0.001
Current influenza vaccine	9,747 (40.3)	1,881 (41.2)	7,866 (40.0)	0.137
Pneumococcal vaccine in last 5 years	9,954 (41.1)	1,756 (38.5)	8,198 (41.7)	<0.001

ARI= acute respiratory infection; ED/UC= emergency department/urgent care; VA= Veterans Affairs

Data are n (%) unless otherwise specified.

All ARI encounters within a 30-day window were considered a single ARI episode. If multiple encounter types occurred during the 30-day window, the highest level of care was used (hospitalization > ED/UC > outpatient).

*The categories under “COVID vaccine status” were categorized as present or absent for each category

**Area deprivation index (ADI) is a measure of socioeconomic disadvantage and was grouped into quintiles from least to most deprived neighborhoods (based on zip code).[51]

***Frailty was defined using the ICD-10 updated Veterans Affairs Frailty Index (VA-FI) and categorized as non-frail (VA-FI ≤ 0.1), prefrail (>0.1–0.2), mildly frail (>0.2–0.3), moderately frail (>0.3–0.4), and severely frail (>0.4).[52]

****Immunocompromised status was based on immunocompromising conditions in the year prior and immunosuppressive medications in the 90 days prior to the ARI episode based on a slightly modified algorithm that has been previously described.[29] Unlike the previously described algorithm, we used diagnosis codes to identify solid organ or hematopoietic stem cell transplantation and HIV/AIDs versus patient registries. Consistent with the previously described algorithm, we required one inpatient or two outpatient diagnosis code for an immunocompromising condition (leukemia, lymphoma, congenital immunodeficiencies, asplenia/hyposplenia, HIV/AIDS, and organ transplant) in the year prior and any

immunosuppressive medication (alkylating agents, antibiotics, antimetbolites, antimitotics, monoclonal antibodies, other, immune-modulating agents, TNF Alpha antagonist, and steroids) with an outpatient days supply or inpatient administration in the 90 days prior.

****Prior COVID-19 infection was defined as any previous documented SARS-CoV-2 infection or no prior documented infection (yes or no).

*****Virtual visit was only assessed among those with an outpatient visit and defined as a virtual visit or not .

*****ICU admission was only assessed among those with a hospital admission and defined as admission to an ICU or not.

Supplemental Table 4. Demographics and clinical characteristics of acute respiratory infection ED/UC visits with SARS-CoV-2 testing, by COVID-19 case-control status

	Total (n=61,976)	**Test-positive COVID-19 cases (n=11,244)**	**Test-negative controls (n=50,732)**	***P*-value**
COVID vaccine status*				<0.001
≥1 dose of BNT162b2 XBB vaccine	3,652 (5.9)	503 (4.5)	3,149 (6.2)	
≥1 dose of BA.4/5-adapted bivalent vaccine	14,756 (23.8)	2,682 (23.9)	12,074 (23.8)	0.905
≥3 doses of original wild-type mRNA vaccine but no bivalent-adapted vaccines	15,718 (25.4)	3,020 (26.9)	12,698 (25.0)	<0.001
≥2 doses of original wild-type mRNA vaccine but no bivalent-adapted vaccines	28,668 (46.3)	5,330 (47.4)	23,338 (46.0)	0.007
No original wild-type mRNA or bivalent-adapted or non-mRNA vaccines	14,572 (23.5)	2,501 (22.2)	12,071 (23.8)	<0.001
Time since last non-XBB adapted vaccine, median days (IQR)	692 (427-838)	697 (431-841)	691 (426-838)	0.017
Age group				0.080

	Total (n=61,976)	**Test-positive COVID-19 cases (n=11,244)**	**Test-negative controls (n=50,732)**	***P*-value**
18–64 years	35,950 (58.0)	6,417 (57.1)	29,533 (58.2)	
65–74 years	13,544 (21.9)	2,502 (22.3)	11,042 (21.8)	
≥75 years	12,482 (20.1)	2,325 (20.7)	10,157 (20.0)	
Sex				0.641
Male	52,249 (84.3)	9,463 (84.2)	42,786 (84.3)	
Female	9,727 (15.7)	1,781 (15.8)	7,946 (15.7)	
Body mass index category				0.005
Underweight (<18.5 kg/m^2)	284 (0.5)	38 (0.3)	246 (0.5)	
Healthy weight (18.5–24.9 kg/m^2)	15,836 (25.5)	2,917 (25.9)	12,919 (25.5)	
Overweight (25–29.9 kg/m^2)	12,969 (20.9)	2,456 (21.8)	10,513 (20.7)	
Obese (≥30 kg/m^2)	32,549 (52.5)	5,779 (51.4)	26,770 (52.8)	
Missing	338 (0.5)	54 (0.5)	284 (0.6)	
Region				<0.001
Midwest	11,847 (19.1)	2,402 (21.4)	9,445 (18.6)	
Northeast	8,560 (13.8)	1,609 (14.3)	6,951 (13.7)	
West	11,811 (19.1)	2,000 (17.8)	9,811 (19.3)	
South	29,758 (48.0)	5,233 (46.5)	24,525 (48.3)	
Race				0.313
Black or African American	17,871 (28.8)	3,251 (28.9)	14,620 (28.8)	

	Total (n=61,976)	**Test-positive COVID-19 cases (n=11,244)**	**Test-negative controls (n=50,732)**	***P*-value**
White	37,239 (60.1)	6,793 (60.4)	30,446 (60.0)	
Other race	6,866 (11.1)	1,200 (10.7)	5,666 (11.2)	
Ethnicity				0.699
Hispanic or Latino	6,244 (10.1)	1,144 (10.2)	5,100 (10.1)	
Not Hispanic or Latino	55,732 (89.9)	10,100 (89.8)	45,632 (89.9)	
Smoking				<0.001
Current or former	29,271 (47.2)	5,169 (46.0)	24,102 (47.5)	
Never smoked	21,978 (35.5)	4,156 (37.0)	17,822 (35.1)	
Unknown	10,727 (17.3)	1,919 (17.1)	8,808 (17.4)	
Area deprivation index (ADI)* Quintile				0.251
1 (Least Deprived)	12,191 (19.7)	2,176 (19.4)	10,015 (19.7)	
2	12,369 (20.0)	2,325 (20.7)	10,044 (19.8)	
3	12,259 (19.8)	2,243 (19.9)	10,016 (19.7)	
4	12,128 (19.6)	2,199 (19.6)	9,929 (19.6)	
5 (Most Deprived)	11,554 (18.6)	2,045 (18.2)	9,509 (18.7)	
Missing	1,475 (2.4)	256 (2.3)	1,219 (2.4)	
VA Frailty index (VA-FI)**				<0.001
Non-frail (VA-FI $\leq$0.1)	27,267 (44.0)	5,002 (44.5)	22,265 (43.9)	

	Total (n=61,976)	**Test-positive COVID-19 cases (n=11,244)**	**Test-negative controls (n=50,732)**	***P*-value**
Pre-frail (VA-FI >0.1-0.2)	16,170 (26.1)	3,059 (27.2)	13,111 (25.8)	
Mildly frail (VA-FI >0.2-0.3)	9,297 (15.0)	1,778 (15.8)	7,519 (14.8)	
Moderately frail (VA-FI >0.3-0.4)	5,047 (8.1)	822 (7.3)	4,225 (8.3)	
Severely frail (VA-FI ≥0.5)	4,195 (6.8)	583 (5.2)	3,612 (7.1)	
Healthcare exposures, 1 year prior Hospital admission	10,609 (17.1)	1,617 (14.4)	8,992 (17.7)	<0.001
Nursing home admission	1,055 (1.7)	199 (1.8)	856 (1.7)	0.54
Intensive care unit admission	2,257 (3.6)	322 (2.9)	1,935 (3.8)	<0.001
Emergency department visit	38,318 (61.8)	6,734 (59.9)	31,584 (62.3)	<0.001
Primary care visit	58,260 (94.0)	10,657 (94.8)	47,603 (93.8)	<0.001
Charlson Comorbidity Index 0	26,471 (42.7)	4,949 (44.0)	21,522 (42.4)	<0.001
1	12,891 (20.8)	2,414 (21.5)	10,477 (20.7)	
2	6,688 (10.8)	1,204 (10.7)	5,484 (10.8)	
3	5,260 (8.5)	964 (8.6)	4,296 (8.5)	
≥ 4	10,666 (17.2)	1,713 (15.2)	8,953 (17.6)	
Immunocompromised***	21,762 (35.1)	3,236 (28.8)	18,526 (36.5)	<0.001

	Total (n=61,976)	**Test-positive COVID-19 cases (n=11,244)**	**Test-negative controls (n=50,732)**	***P*-value**
Week of infection				<0.001
Sep 25–Sep 30,2023	2,095 (3.4)	376 (3.3)	1,719 (3.4)	
Oct 01–Oct 07, 2023	2,291 (3.7)	360 (3.2)	1,931 (3.8)	
Oct 08–Oct 14, 2023	2,251 (3.6)	358 (3.2)	1,893 (3.7)	
Oct 15–Oct 21, 2023	2,276 (3.7)	366 (3.3)	1,910 (3.8)	
Oct 22–Oct 28, 2023	2,318 (3.7)	348 (3.1)	1,970 (3.9)	
Oct 29–Nov 04, 2023	2,304 (3.7)	342 (3.0)	1,962 (3.9)	
Nov 05–Nov 11, 2023	2,496 (4.0)	399 (3.5)	2,097 (4.1)	
Nov 12–Nov 18, 2023	3,019 (4.9)	518 (4.6)	2,501 (4.9)	
Nov 19–Nov 25, 2023	2,957 (4.8)	539 (4.8)	2,418 (4.8)	
Nov 26–Dec 02, 2023	3,684 (5.9)	629 (5.6)	3,055 (6.0)	
Dec 03–Dec 09, 2023	3,779 (6.1)	696 (6.2)	3,083 (6.1)	
Dec 10–Dec 16, 2023	3,918 (6.3)	729 (6.5)	3,189 (6.3)	
Dec 17–Dec 23, 2023	4,874 (7.9)	920 (8.2)	3,954 (7.8)	
Dec 24–Dec 30, 2023	5,371 (8.7)	1,107 (9.8)	4,264 (8.4)	
Dec 31, 2023–Jan 06, 2024	5,332 (8.6)	1,023 (9.1)	4,309 (8.5)	
Jan 07–Jan 13, 2024	4,257 (6.9)	844 (7.5)	3,413 (6.7)	
Jan 14–Jan 20, 2024	3,139 (5.1)	644 (5.7)	2,495 (4.9)	
Jan 21–Jan 27, 2024	3,518 (5.7)	674 (6.0)	2,844 (5.6)	

	Total (n=61,976)	**Test-positive COVID-19 cases (n=11,244)**	**Test-negative controls (n=50,732)**	***P*-value**
Jan 28–Jan 31, 2024	2,097 (3.4)	372 (3.3)	1,725 (3.4)	
Prior COVID-19 infection****	18,505 (29.9)	2,995 (26.6)	15,510 (30.6)	<0.001
Current influenza vaccine	19,718 (31.8)	3,734 (33.2)	15,984 (31.5)	<0.001
Pneumococcal vaccine in last 5 years	21,138 (34.1)	3,771 (33.5)	17,367 (34.2)	0.160

ARI= acute respiratory infection; ED/UC= emergency department/urgent care; VA= Veterans Affairs

Data are n (%) unless otherwise specified.

All ARI encounters within a 30-day window were considered a single ARI episode. If multiple encounter types occurred during the 30-day window, the highest level of care was used (hospitalization > ED/UC > outpatient).

*The categories under “COVID vaccine status” were categorized as present or absent for each category

**Area deprivation index (ADI) is a measure of socioeconomic disadvantage and was grouped into quintiles from least to most deprived neighborhoods (based on zip code).[51]

***Frailty was defined using the ICD-10 updated Veterans Affairs Frailty Index (VA-FI) and categorized as non-frail (VA-FI ≤ 0.1), prefrail (>0.1–0.2), mildly frail (>0.2–0.3), moderately frail (>0.3–0.4), and severely frail (>0.4).[52]

****Immunocompromised status was based on immunocompromising conditions in the year prior and immunosuppressive medications in the 90 days prior to the ARI episode based on a slightly modified algorithm that has been previously described.[29] Unlike the previously described algorithm, we used diagnosis codes to identify solid organ or hematopoietic stem cell transplantation and HIV/AIDs versus patient registries. Consistent with the previously described algorithm, we required one inpatient or two outpatient diagnosis code for an immunocompromising condition (leukemia, lymphoma, congenital immunodeficiencies, asplenia/hyposplenia, HIV/AIDS, and organ transplant) in the year prior and any immunosuppressive medication (alkylating agents, antibiotics, antimetbolites, antimitotics,

monoclonal antibodies, other, immune-modulating agents, TNF Alpha antagonist, and steroids) with an outpatient days supply or inpatient administration in the 90 days prior.

****Prior COVID-19 infection was defined as any previous documented SARS-CoV-2 infection or no prior documented infection (yes or no).

*****Virtual visit was only assessed among those with an outpatient visit and defined as a virtual visit or not .

*****ICU admission was only assessed among those with a hospital admission and defined as admission to an ICU or not.

Supplemental Table 5. Demographics and clinical characteristics of acute respiratory infection outpatient visits with SARS-CoV-2 testing, by COVID-19 case-control status

	Total (n=26,992)	**Test-positive COVID-19 cases (n=4,718)**	**Test-negative controls (n=22,274)**	***P*-value**
COVID vaccine status*	1,836 (6.8)	259 (5.5)	1,577 (7.1)	<0.001
≥1 dose of BNT162b2 XBB vaccine				
≥1 dose of BA.4/5-adapted bivalent vaccine	7,335 (27.2)	1,191 (25.2)	6,144 (27.6)	0.001
≥3 doses of original wild-type mRNA vaccine but no bivalent-adapted vaccines	6,933 (25.7)	1,229 (26.0)	5,704 (25.6)	0.529
≥2 doses of original wild-type mRNA vaccine but no bivalent-adapted vaccines	12,167 (45.1)	2,171 (46.0)	9,996 (44.9)	0.154
No original wild-type mRNA or bivalent-adapted or non-mRNA vaccines	5,825 (21.6)	1,041 (22.1)	4,784 (21.5)	0.374
Time since last non-XBB adapted vaccine, median days (IQR)	661 (409-819)	679 (424-837)	657 (406-817)	<0.001
Age group				<0.001

	Total (n=26,992)	**Test-positive COVID-19 cases (n=4,718)**	**Test-negative controls (n=22,274)**	***P*-value**
18–64 years	13,175 (48.8)	2,599 (55.1)	10,576 (47.5)	
65–74 years	6,601 (24.5)	1,029 (21.8)	5,572 (25.0)	
≥75 years	7,216 (26.7)	1,090 (23.1)	6,126 (27.5)	
Sex				0.001
Male	23,153 (85.8)	3,977 (84.3)	19,176 (86.1)	
Female	3,839 (14.2)	741 (15.7)	3,098 (13.9)	
Body mass index category				<0.001
Underweight (<18.5 kg/m^2)	314 (1.2)	28 (0.6)	286 (1.3)	
Healthy weight (18.5–24.9 kg/m^2)	8,013 (29.7)	1,285 (27.2)	6,728 (30.2)	
Overweight (25–29.9 kg/m^2)	5,473 (20.3)	1,063 (22.5)	4,410 (19.8)	
Obese (≥30 kg/m^2)	13,048 (48.3)	2,299 (48.7)	10,749 (48.3)	
Missing	144 (0.5)	43 (0.9)	101 (0.4)	
Region				<0.001
Midwest	5,881 (21.8)	1,217 (25.8)	4,664 (20.9)	
Northeast	3,390 (12.6)	633 (13.4)	2,757 (12.4)	
West	4,665 (17.3)	762 (16.2)	3,903 (17.5)	
South	13,056 (48.4)	2,106 (44.6)	10,950 (49.2)	
Race				0.001
Black or African American	6,129 (22.7)	1,080 (22.9)	5,049 (22.7)	

	Total (n=26,992)	**Test-positive COVID-19 cases (n=4,718)**	**Test-negative controls (n=22,274)**	***P*-value**
White	17,829 (66.1)	3,039 (64.4)	14,790 (66.4)	
Other race	3,034 (11.2)	599 (12.7)	2,435 (10.9)	
Ethnicity				0.724
Hispanic or Latino	2,515 (9.3)	446 (9.5)	2,069 (9.3)	
Not Hispanic or Latino	24,477 (90.7)	4,272 (90.5)	20,205 (90.7)	
Smoking				<0.001
Current or former	13,988 (51.8)	2,232 (47.3)	11,756 (52.8)	
Never smoked	8,856 (32.8)	1,690 (35.8)	7,166 (32.2)	
Unknown	4,148 (15.4)	796 (16.9)	3,352 (15.0)	
Area deprivation index (ADI)*				0.142
Quintile				
1 (Least Deprived)	5,443 (20.2)	952 (20.2)	4,491 (20.2)	
2	5,367 (19.9)	949 (20.1)	4,418 (19.8)	
3	5,273 (19.5)	973 (20.6)	4,300 (19.3)	
4	5,239 (19.4)	908 (19.2)	4,331 (19.4)	
5 (Most Deprived)	5,298 (19.6)	868 (18.4)	4,430 (19.9)	
Missing	372 (1.4)	68 (1.4)	304 (1.4)	
VA Frailty index (VA-FI)**				<0.001
Non-frail (VA-FI $\leq$0.1)	9,358 (34.7)	2,110 (44.7)	7,248 (32.5)	
Pre-frail (VA-FI >0.1-0.2)	6,573 (24.3)	1,263 (26.8)	5,310 (23.8)	

	Total (n=26,992)	**Test-positive COVID-19 cases (n=4,718)**	**Test-negative controls (n=22,274)**	***P*-value**
Mildly frail (VA-FI >0.2-0.3)	4,497 (16.7)	671 (14.2)	3,826 (17.2)	
Moderately frail (VA-FI >0.3-0.4)	3,004 (11.1)	361 (7.7)	2,643 (11.9)	
Severely frail (VA-FI ≥0.5)	3,560 (13.2)	313 (6.6)	3,247 (14.6)	
Healthcare exposures, 1 year prior Hospital admission	9,141 (33.9)	865 (18.3)	8,276 (37.2)	<0.001
Nursing home admission	1,596 (5.9)	403 (8.5)	1,193 (5.4)	<0.001
Intensive care unit admission	2,935 (10.9)	219 (4.6)	2,716 (12.2)	<0.001
Emergency department visit	13,996 (51.9)	1,745 (37.0)	12,251 (55.0)	<0.001
Primary care visit	25,500 (94.5)	4,392 (93.1)	21,108 (94.8)	<0.001
Charlson Comorbidity Index 0	9,120 (33.8)	2,087 (44.2)	7,033 (31.6)	<0.001
1	5,106 (18.9)	969 (20.5)	4,137 (18.6)	
2	3,095 (11.5)	489 (10.4)	2,606 (11.7)	
3	2,571 (9.5)	388 (8.2)	2,183 (9.8)	
≥ 4	7,100 (26.3)	785 (16.6)	6,315 (28.4)	
Immunocompromised***	8,125 (30.1)	977 (20.7)	7,148 (32.1)	<0.001
Week of infection Sep 25–Sep 30,2023	2,247 (8.3)	337 (7.1)	1,910 (8.6)	<0.001

	Total (n=26,992)	**Test-positive COVID-19 cases (n=4,718)**	**Test-negative controls (n=22,274)**	***P*-value**
Oct 01–Oct 07, 2023	1,312 (4.9)	185 (3.9)	1,127 (5.1)	
Oct 08–Oct 14, 2023	975 (3.6)	131 (2.8)	844 (3.8)	
Oct 15–Oct 21, 2023	1,157 (4.3)	203 (4.3)	954 (4.3)	
Oct 22–Oct 28, 2023	1,146 (4.3)	165 (3.5)	981 (4.4)	
Oct 29–Nov 04, 2023	1,096 (4.1)	165 (3.5)	931 (4.2)	
Nov 05–Nov 11, 2023	1,043 (3.9)	137 (2.9)	906 (4.1)	
Nov 12–Nov 18, 2023	1,292 (4.8)	193 (4.1)	1,099 (4.9)	
Nov 19–Nov 25, 2023	1,038 (3.8)	172 (3.6)	866 (3.9)	
Nov 26–Dec 02, 2023	1,670 (6.2)	293 (6.2)	1,377 (6.2)	
Dec 03–Dec 09, 2023	1,568 (5.8)	288 (6.1)	1,280 (5.7)	
Dec 10–Dec 16, 2023	1,671 (6.2)	329 (7.0)	1,342 (6.0)	
Dec 17–Dec 23, 2023	1,813 (6.7)	387 (8.2)	1,426 (6.4)	
Dec 24–Dec 30, 2023	1,474 (5.5)	297 (6.3)	1,177 (5.3)	
Dec 31, 2023–Jan 06, 2024	1,789 (6.6)	391 (8.3)	1,398 (6.3)	
Jan 07–Jan 13, 2024	1,830 (6.8)	336 (7.1)	1,494 (6.7)	
Jan 14–Jan 20, 2024	1,299 (4.8)	259 (5.5)	1,040 (4.7)	
Jan 21–Jan 27, 2024	1,607 (6.0)	291 (6.2)	1,316 (5.9)	
Jan 28–Jan 31, 2024	965 (3.6)	159 (3.4)	806 (3.6)	
Prior COVID-19 infection****	6,620 (24.5)	1,003 (21.3)	5,617 (25.2)	<0.001

	Total (n=26,992)	**Test-positive COVID-19 cases (n=4,718)**	**Test-negative controls (n=22,274)**	***P*-value**
Virtual visit (outpatient only)*****	2,773 (10.3)	1,129 (23.9)	1,644 (7.4)	<0.001
Current influenza vaccine	9,612 (35.6)	1,685 (35.7)	7,927 (35.6)	0.87
Pneumococcal vaccine in last 5 years	9,940 (36.8)	1,589 (33.7)	8,351 (37.5)	<0.001

ARI= acute respiratory infection; ED/UC= emergency department/urgent care; VA= Veterans Affairs

Data are n (%) unless otherwise specified.

All ARI encounters within a 30-day window were considered a single ARI episode. If multiple encounter types occurred during the 30-day window, the highest level of care was used (hospitalization > ED/UC > outpatient).

*The categories under "COVID vaccine status" were categorized as present or absent for each category

**Area deprivation index (ADI) is a measure of socioeconomic disadvantage and was grouped into quintiles from least to most deprived neighborhoods (based on zip code).[51]

***Frailty was defined using the ICD-10 updated Veterans Affairs Frailty Index (VA-FI) and categorized as non-frail (VA-FI ≤ 0.1), prefrail (>0.1–0.2), mildly frail (>0.2–0.3), moderately frail (>0.3–0.4), and severely frail (>0.4).[52]

****Immunocompromised status was based on immunocompromising conditions in the year prior and immunosuppressive medications in the 90 days prior to the ARI episode based on a slightly modified algorithm that has been previously described.[29] Unlike the previously described algorithm, we used diagnosis codes to identify solid organ or hematopoietic stem cell transplantation and HIV/AIDs versus patient registries. Consistent with the previously described algorithm, we required one inpatient or two outpatient diagnosis code for an immunocompromising condition (leukemia, lymphoma, congenital immunodeficiencies, asplenia/hyposplenia, HIV/AIDS, and organ transplant) in the year prior and any immunosuppressive medication (alkylating agents, antibiotics, antimetbolites, antimitotics,

monoclonal antibodies, other, immune-modulating agents, TNF Alpha antagonist, and steroids) with an outpatient days supply or inpatient administration in the 90 days prior.

****Prior COVID-19 infection was defined as any previous documented SARS-CoV-2 infection or no prior documented infection (yes or no).

*****Virtual visit was only assessed among those with an outpatient visit and defined as a virtual visit or not .

*****ICU admission was only assessed among those with a hospital admission and defined as admission to an ICU or not.

Supplemental Table 6. Demographics and clinical characteristics of acute respiratory infection episodes (hospitalization, ED/UC visits, outpatient visits) with SARS-CoV-2 testing, by vaccination status

Variable	Total (n=113,174)	Received BNT162b2 XBB vaccine (n=7,324)	No XBB vaccine of any kind (n=105,850)	*P*-value
COVID vaccine status ≥1 dose of BA.4/5-adapted bivalent vaccine	29,907 (26.4)	5,626 (76.8)	24,281 (22.9)	<0.001
≥3 doses of original wild-type mRNA vaccine but no bivalent-adapted vaccines	29,463 (26.0)	1,262 (17.2)	28,201 (26.6)	<0.001
≥2 doses of original wild-type mRNA vaccine but no bivalent-adapted vaccines	51,546 (45.6)	1,499 (20.5)	50,047 (47.3)	<0.001
No original wild-type mRNA or bivalent-adapted or non-mRNA vaccines	24,747 (21.9)	106 (1.4)	24,641 (23.3)	<0.001
Time since last non-XBB adapted vaccine, median days (IQR)	670 (413–820)	433 (385–477)	691 (421–840)	<0.001
Age group 18–64 years	54,563 (48.2)	1,811 (24.7)	52,752 (49.8)	<0.001
65–74 years	27,821 (24.6)	2,416 (33)	25,405 (24)	
≥75 years	30,790 (27.2)	3,097 (42.3)	27,693 (26.2)	
Sex Male	98,172 (86.7)	6,644 (90.7)	91,528 (86.5)	<0.001
Female	15,002 (13.3)	680 (9.3)	14,322 (13.5)	
Body mass index category Underweight (<18.5 kg/m^2)	1,399 (1.2)	64 (0.9)	1,335 (1.3)	<0.001

Variable	Total (n=113,174)	Received BNT162b2 XBB vaccine (n=7,324)	No XBB vaccine of any kind (n=105,850)	*P*-value
Healthy weight (18.5–24.9 kg/m^2)	34,083 (30.1)	2,252 (30.7)	31,831 (30.1)	
Overweight (25–29.9 kg/m^2)	22,780 (20.2)	1,571 (21.5)	21,209 (20)	
Obese ($\geq$30 kg/m^2)	54,398 (48.3)	3,429 (46.8)	50,969 (48.2)	
Region				<0.001
Midwest	22,167 (19.6)	1,830 (25)	20,337 (19.2)	
Northeast	15,063 (13.3)	1,050 (14.3)	14,013 (13.2)	
West	21,933 (19.4)	1,458 (19.9)	20,475 (19.3)	
South	54,011 (47.7)	2,986 (40.8)	51,025 (48.2)	
Race				<0.001
Black or African American	29,699 (26.2)	2,301 (31.4)	27,398 (25.9)	
White	71,345 (63.0)	4,337 (59.2)	67,008 (63.3)	
Other race	12,130 (10.7)	686 (9.4)	11,444 (10.8)	
Ethnicity				<0.001
Hispanic or Latino	10,527 (9.3)	472 (6.4)	10,055 (9.5)	
Not Hispanic or Latino	102,647 (90.7)	6,852 (93.6)	95,795 (90.5)	
Smoking				<0.001
Current or former	58,062 (51.3)	4,122 (56.3)	53,940 (51)	
Area deprivation index (ADI) Quintile				<0.001
1 (Least Deprived)	22,140 (19.6)	1,845 (25.2)	20,295 (19.2)	
2	22,134 (19.6)	1,396 (19.1)	20,738 (19.6)	
3	22,143 (19.6)	1,357 (18.5)	20,786 (19.6)	
4	22,126 (19.6)	1,243 (17)	20,883 (19.7)	
5 (Most Deprived)	22,136 (19.6)	1,415 (19.3)	20,721 (19.6)	
VA Frailty index (VA-FI)*				<0.001
Non-frail (VA-FI $\leq$0.1)	40,182 (35.5)	1,435 (19.6)	38,747 (36.6)	

Variable	Total (n=113,174)	Received BNT162b2 XBB vaccine (n=7,324)	No XBB vaccine of any kind (n=105,850)	*P*-value
Pre-frail (VA-FI >0.1-0.2)	27,422 (24.2)	1,721 (23.5)	25,701 (24.3)	
Mildly frail (VA-FI >0.2-0.3)	18,818 (16.6)	1,597 (21.8)	17,221 (16.3)	
Moderately frail (VA-FI >0.3-0.4)	12,559 (11.1)	1,129 (15.4)	11,430 (10.8)	
Severely frail (VA-FI ≥0.5)	14,193 (12.5)	1,442 (19.7)	12,751 (12)	
Healthcare exposures, 1 year prior Hospital admission	32,067 (28.3)	2,599 (35.5)	29,468 (27.8)	<0.001
Nursing home admission	3,924 (3.5)	325 (4.4)	3,599 (3.4)	<0.001
Intensive care unit admission	8,825 (7.8)	685 (9.4)	8,140 (7.7)	<0.001
Emergency department visit	69,978 (61.8)	4,797 (65.5)	65,181 (61.6)	<0.001
Primary care visit	106,691 (94.3)	7,165 (97.8)	99,526 (94)	<0.001
Charlson Comorbidity Index 0	38,598 (34.1)	1,370 (18.7)	37,228 (35.2)	<0.001
1	21,698 (19.2)	1,268 (17.3)	20,430 (19.3)	
2	12,962 (11.5)	952 (13)	12,010 (11.3)	
3	10,833 (9.6)	919 (12.5)	9,914 (9.4)	
≥ 4	29,083 (25.7)	2,815 (38.4)	26,268 (24.8)	
Immunocompromised**	40,309 (35.6)	2,961 (40.4)	37,348 (35.3)	<0.001
Medical History*** Acute cerebrovascular disease	5,372 (4.7)	467 (6.4)	4,905 (4.6)	<0.001
Acute myocardial infarction	3,842 (3.4)	301 (4.1)	3,541 (3.3)	<0.001
Alcohol and substance related disorders	28,011 (24.8)	1,672 (22.8)	26,339 (24.9)	<0.001
Any cancer or malignancy	42,527 (37.6)	3,695 (50.5)	38,832 (36.7)	<0.001

Variable	Total (n=113,174)	Received BNT162b2 XBB vaccine (n=7,324)	No XBB vaccine of any kind (n=105,850)	*P*-value
Aortic and peripheral arterial embolism or thrombosis	440 (0.4)	47 (0.6)	393 (0.4)	<0.001
Asthma	10,024 (8.9)	759 (10.4)	9,265 (8.8)	<0.001
Benign prostatic hyperplasia	23,037 (20.4)	2,201 (30.1)	20,836 (19.7)	<0.001
Cardiac dysrhythmias	27,478 (24.3)	2,304 (31.5)	25,174 (23.8)	<0.001
Chronic kidney disease	13,161 (11.6)	1,313 (17.9)	11,848 (11.2)	<0.001
Chronic obstructive pulmonary disease and bronchiectasis	26,259 (23.2)	2,247 (30.7)	24,012 (22.7)	<0.001
Congestive heart failure	17,429 (15.4)	1,589 (21.7)	15,840 (15)	<0.001
Coronary atherosclerosis and other heart disease	25,404 (22.4)	2,225 (30.4)	23,179 (21.9)	<0.001
Delirium, dementia, and other cognitive disorders	9,559 (8.4)	882 (12)	8,677 (8.2)	<0.001
Diabetes with or without chronic complications	47,147 (41.7)	3,885 (53)	43,262 (40.9)	<0.001
Epilepsy	3,142 (2.8)	228 (3.1)	2,914 (2.8)	0.070
Human immunodeficiency virus (HIV) infection	1,271 (1.1)	140 (1.9)	1,131 (1.1)	<0.001
Hypertension	66,411 (58.7)	5,339 (72.9)	61,072 (57.7)	<0.001
Influenza	1,413 (1.2)	65 (0.9)	1,348 (1.3)	0.004
Liver diseases	10,877 (9.6)	827 (11.3)	10,050 (9.5)	<0.001
Mental health conditions	57,479 (50.8)	3,571 (48.8)	53,908 (50.9)	<0.001
Osteoarthritis	23,617 (20.9)	2,105 (28.7)	21,512 (20.3)	<0.001
Peripheral and visceral atherosclerosis	9,699 (8.6)	926 (12.6)	8,773 (8.3)	<0.001
Pneumonia	9,596 (8.5)	774 (10.6)	8,822 (8.3)	<0.001
Pulmonary heart disease	7,598 (6.7)	674 (9.2)	6,924 (6.5)	<0.001

Variable	Total (n=113,174)	Received BNT162b2 XBB vaccine (n=7,324)	No XBB vaccine of any kind (n=105,850)	*P*-value
Rheumatoid arthritis	2,273 (2.0)	220 (3)	2,053 (1.9)	<0.001
Septicemia	4,805 (4.2)	390 (5.3)	4,415 (4.2)	<0.001
Thyroid disorder	14,098 (12.5)	1,113 (15.2)	12,985 (12.3)	<0.001
Tuberculosis	237 (0.2)	21 (0.3)	216 (0.2)	0.134
Week of infection Sep 25–Sep 30,2023	5,503 (4.9)	< 5 (<0.1)	5,503 (5.2)	<0.001
Oct 01–Oct 07, 2023	4,834 (4.3)	6 (0.1)	4,828 (4.6)	
Oct 08–Oct 14, 2023	4,358 (3.9)	7 (0.1)	4,351 (4.1)	
Oct 15–Oct 21, 2023	4,707 (4.2)	31 (0.4)	4,676 (4.4)	
Oct 22–Oct 28, 2023	4,624 (4.1)	74 (1)	4,550 (4.3)	
Oct 29–Nov 04, 2023	4,453 (3.9)	121 (1.7)	4,332 (4.1)	
Nov 05–Nov 11, 2023	4,741 (4.2)	201 (2.7)	4,540 (4.3)	
Nov 12–Nov 18, 2023	5,622 (5.0)	291 (4)	5,331 (5)	
Nov 19–Nov 25, 2023	5,155 (4.6)	320 (4.4)	4,835 (4.6)	
Nov 26–Dec 02, 2023	6,746 (6.0)	474 (6.5)	6,272 (5.9)	
Dec 03–Dec 09, 2023	6,855 (6.1)	524 (7.2)	6,331 (6)	
Dec 10–Dec 16, 2023	6,959 (6.1)	568 (7.8)	6,391 (6)	
Dec 17–Dec 23, 2023	8,160 (7.2)	680 (9.3)	7,480 (7.1)	
Dec 24–Dec 30, 2023	8,366 (7.4)	792 (10.8)	7,574 (7.2)	
Dec 31, 2023–Jan 06, 2024	8,814 (7.8)	871 (11.9)	7,943 (7.5)	
Jan 07–Jan 13, 2024	7,624 (6.7)	759 (10.4)	6,865 (6.5)	
Jan 14–Jan 20, 2024	5,663 (5.0)	579 (7.9)	5,084 (4.8)	
Jan 21–Jan 27, 2024	6,316 (5.6)	623 (8.5)	5,693 (5.4)	
Jan 28–Jan 31, 2024	3,674 (3.2)	403 (5.5)	3,271 (3.1)	
Prior COVID-19 infection	31,195 (27.6)	1,936 (26.4)	29,259 (27.6)	0.025
Virtual visit (outpatient only)	2,773 (10.3)	204 (11.1)	2,569 (10.2)	0.221

Variable	Total (n=113,174)	Received BNT162b2 XBB vaccine (n=7,324)	No XBB vaccine of any kind (n=105,850)	*P*-value
ICU admission (hospitalized only)	4,955 (20.5)	370 (20.2)	4,585 (20.5)	0.726
Current influenza vaccine	39,077 (34.5)	6,779 (92.6)	32,298 (30.5)	<0.001
Pneumococcal vaccine in last 5 years	41,032 (36.3)	3,801 (51.9)	37,231 (35.2)	<0.001

ARI= acute respiratory infection; ED/UC= emergency department/urgent care; VA= Veterans Affairs

Data are n (%) unless otherwise specified.

All ARI encounters within a 30-day window were considered a single ARI episode. If multiple encounter types occurred during the 30-day window, the highest level of care was used (hospitalization > ED/UC > outpatient).

*VA Frailty index was categorized as non-frail (VA-FI ≤ 0.1), prefrail (>0.1–0.2), mildly frail (>0.2–0.3), moderately frail (>0.3–0.4), and severely frail (>0.4)

**Immunocompromised status was based on immunocompromising conditions in the year prior and immunosuppressive medications in the 90 days prior to the ARI episode based on a slightly modified algorithm that has been previously described. (Tartof SY, et al. Lancet Reg Health Am. 2022:9:100198.) Unlike the previously described algorithm, we used diagnosis codes to identify solid organ or hematopoietic stem cell transplantation and HIV/AIDs versus patient registries. Consistent with the previously described algorithm, we required one inpatient or two outpatient diagnosis code for an immunocompromising condition (leukemia, lymphoma, congenital immunodeficiencies, asplenia/hyposplenia, HIV/AIDS, and organ transplant) in the year prior and any immunosuppressive medication (alkylating agents, antibiotics, antimetbolites, antimitotics, monoclonal antibodies, other, immune-modulating agents, TNF Alpha antagonist, and steroids) with an outpatient days supply or inpatient administration in the 90 days prior.

***Medical history included underlying conditions and diagnoses in the year prior to the ARI episode, identified using international classification of diseases (ICD)-10 codes.

Supplemental Table 7. Adjusted vaccine effectiveness of the BNT162b2 XBB vaccine for hospitalization, ED/UC visits, and outpatient visits by age group

Outcome	Age ≥65 years (n = 58,611)		Age <65 years (n = 54,563)	
	VE (95% CI)	Median (IQR) days since XBB vaccine	VE (95% CI)	Median (IQR) days since XBB vaccine
Hospitalization	41 (32–50)	54 (33–74)	58 (33–73)	50 (34–67)
ED/UC visit	35 (27–43)	56 (36–77)	48 (37–57)	54 (35–74)
Outpatient visit	24 (9–36)	53 (35–76)	34 (14–50)	51 (33–75)

CI= confidence interval; ED/UC= emergency department/urgent care; IQR= interquartile range; VA= Veterans Affairs; VE = vaccine effectiveness

Compared the odds of receiving a BNT162b2 XBB vaccine between SARS-CoV-2 positive cases and SARS-CoV-2 negative controls. Adjusted for week of ARI episode, age, sex, race, ethnicity, BMI category, Charlson Comorbidity Index, receipt of 2023–2024 influenza vaccine, receipt of pneumococcal vaccine in the past 5 years, interactions with healthcare systems in the year prior, previous SARS-CoV-2 infection, smoking status, immunocompromised status, and Census region.

Supplemental Table 8. Adjusted vaccine effectiveness of the BNT162b2 XBB vaccine for hospitalization, ED/UC visits, and outpatient visits by immunocompromised status

Outcome	Immunocompromised (*n* = 40,309)		Not Immunocompromised (*n* = 72,865)	
	VE (95% CI)	Median (IQR) days since XBB vaccine	VE (95% CI)	Median (IQR) days since XBB vaccine
Hospitalization	33 (16–47)	52 (33–73)	49 (38–58)	54 (34–74)
ED/UC visit	34 (22–45)	55 (35–74)	42 (34–49)	56 (36–77)
Outpatient visit	40 (19–55)	54 (35–77)	22 (8–34)	52 (34–75)

CI= confidence interval; ED/UC= emergency department/urgent care; IQR= interquartile range; VA= Veterans Affairs; VE = vaccine effectiveness

Compared the odds of receiving a BNT162b2 XBB vaccine between SARS-CoV-2 positive cases and SARS-CoV-2 negative controls. Adjusted for week of ARI episode, age, sex, race, ethnicity, BMI category, Charlson Comorbidity Index, receipt of 2023–2024 influenza vaccine, receipt of pneumococcal vaccine in the past 5 years, interactions with healthcare systems in the year prior, previous SARS-CoV-2 infection, smoking status, immunocompromised status, and Census region.

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Supplemental Table 9. Adjusted vaccine effectiveness of the BNT162b2 XBB vaccine for hospitalization, ED/UC visits, and outpatient visits by obesity classification

Outcome	Obese (*n* = 54,398)		Non-obese (*n* = 58,262)	
	VE (95% CI)	Median (IQR) days since XBB vaccine	VE (95% CI)	Median (IQR) days since XBB vaccine
Hospitalization	50 (36–61)	52 (33–74)	39 (27–49)	53 (34–73)
ED/UC visit	44 (35–52)	56 (36–76)	35 (25–43)	56 (36–76)
Outpatient visit	34 (19–47)	54 (35–76)	21 (3–35)	52 (34–76)

CI= confidence interval; ED/UC= emergency department/urgent care; IQR= interquartile range; VA= Veterans Affairs; VE = vaccine effectiveness

Compared the odds of receiving a BNT162b2 XBB vaccine between SARS-CoV-2 positive cases and SARS-CoV-2 negative controls. Adjusted for week of ARI episode, age, sex, race, ethnicity, BMI category, Charlson Comorbidity Index, receipt of 2023–2024 influenza vaccine, receipt of pneumococcal vaccine in the past 5 years, interactions with healthcare systems in the year prior, previous SARS-CoV-2 infection, smoking status, immunocompromised status, and Census region.

Supplemental Table 10. Adjusted vaccine effectiveness of the BNT162b2 XBB vaccine for hospitalization, ED/UC visits, and outpatient visits by smoking status

Outcome	Current or former smoker (*n* = 58,062)		Non-smoker (*n* = 55,112)	
	VE (95% CI)	Median (IQR) days since XBB vaccine	VE (95% CI)	Median (IQR) days since XBB vaccine
Hospitalization	38 (26–48)	53 (34–73)	51 (38–62)	53 (33–75)
ED/UC visit	43 (35–51)	55 (35–76)	34 (24–43)	56 (37–77)
Outpatient visit	32 (17–45)	52 (33–74)	22 (4–36)	54 (36–77)

CI= confidence interval; ED/UC= emergency department/urgent care; IQR= interquartile range; VA= Veterans Affairs; VE = vaccine effectiveness

Compared the odds of receiving a BNT162b2 XBB vaccine between SARS-CoV-2 positive cases and SARS-CoV-2 negative controls. Adjusted for week of ARI episode, age, sex, race, ethnicity, BMI category, Charlson Comorbidity Index, receipt of 2023–2024 influenza vaccine, receipt of pneumococcal vaccine in the past 5 years, interactions with healthcare systems in the year prior, previous SARS-CoV-2 infection, smoking status, immunocompromised status, and Census region.

Supplemental Table 11. Adjusted vaccine effectiveness of the BNT162b2 XBB vaccine for hospitalization, ED/UC visits, and outpatient visits among those with 1 or more doses of BA.4/5-adapted bivalent vaccine

Outcome	VE (95% CI)
Hospitalization[1]	45 (34-54)
ED/UC visit[2]	44 (37-51)
Outpatient visit[3]	26 (11-39)

CI= confidence interval; ED/UC= emergency department/urgent care; VE= vaccine effectiveness

Compared the odds of receiving a BNT162b2 XBB vaccine between SARS-CoV-2 positive cases and SARS-CoV-2 negative controls. Adjusted for week of ARI episode, age, sex, race, ethnicity, BMI category, Charlson Comorbidity Index, receipt of 2023-2024 influenza vaccine, receipt of pneumococcal vaccine in the past 5 years, interactions with healthcare systems in the year prior, previous SARS-CoV-2 infection, smoking status, immunocompromised status, and Census region.

[1] Stratified analysis: 200 XBB / 1,443 cases (13.9%), 1,194 XBB / 6,373 controls (18.7%). Non-stratified analysis: 257 XBB / 4,561 cases (5.6%), 1,579 XBB / 19,645 controls (8.0%).

[2] Stratified analysis: 387 XBB / 2,682 cases (14.4%), 2,439 XBB / 12,074 controls (20.2%). Non-stratified analysis: 503 XBB / 11,244 cases (4.5%), 3,149 XBB / 50,732 controls (6.2%).

[3] Stratified analysis: 204 XBB / 1,191 cases (17.1%), 1,202 XBB / 6,144 controls (19.6%). Non-stratified analysis: 259 XBB / 4,718 cases (5.5%), 1,577 XBB / 22,274 controls (7.1%).

Supplemental Table 12. Adjusted vaccine effectiveness of the BNT162b2 XBB vaccine for hospitalization, ED/UC visits, and outpatient visits among those with 3 or more doses of original wild-type mRNA but no bivalent-adapted vaccines

Outcome	VE (95% CI)
Hospitalization[1]	56 (36-69)
ED/UC visit[2]	41 (25-53)
Outpatient visit[3]	38 (11-57)

CI= confidence interval; ED/UC= emergency department/urgent care; VE= vaccine effectiveness

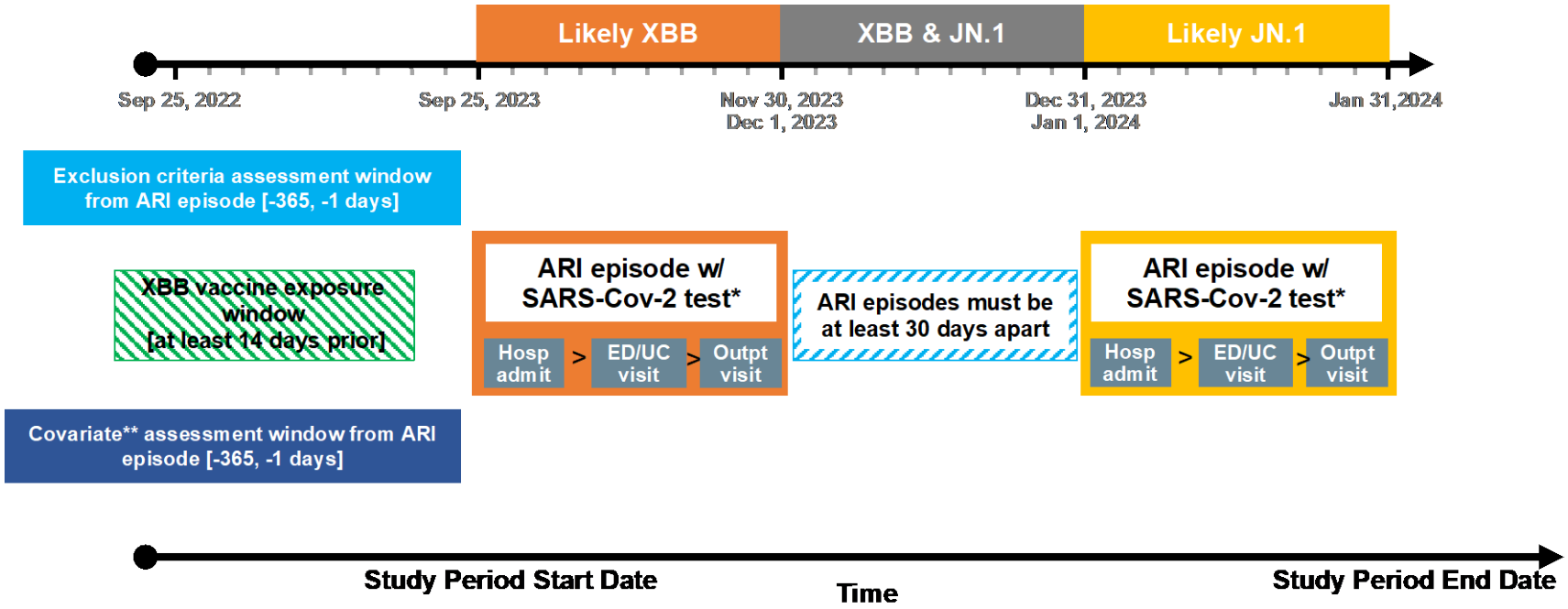
Compared the odds of receiving a BNT162b2 XBB vaccine between SARS-CoV-2 positive cases and SARS-CoV-2 negative controls. Adjusted for week of ARI episode, age, sex, race, ethnicity, BMI category, Charlson Comorbidity Index, receipt of 2023-2024 influenza vaccine, receipt of pneumococcal vaccine in the past 5 years, interactions with healthcare systems in the year prior, previous SARS-CoV-2 infection, smoking status, immunocompromised status, and Census region.

[1] Stratified analysis: 36 XBB / 1,263 cases (2.8%), 296 XBB / 5,549 controls (5.3%). Non-stratified analysis: 257 XBB / 4,561 cases (5.6%), 1,579 XBB / 19,645 controls (8.0%).

[2] Stratified analysis: 87 XBB / 3,020 cases (2.9%), 540 XBB / 12,698 controls (4.2%). Non-stratified analysis: 503 XBB / 11,244 cases (4.5%), 3,149 XBB / 50,732 controls (6.2%).

[3] Stratified analysis: 39 XBB / 1,229 cases (3.2%), 264 XBB / 5,704 controls (4.6%). Non-stratified analysis: 259 XBB / 4,718 cases (5.5%), 1,577 XBB / 22,274 controls (7.1%).

Supplemental Figure 1. Study timeframes for assessing exclusion, exposure, covariates and acute respiratory infection episodes



All ARI encounters (hospitalization, emergency department / urgent care (ED/UC) visit, or outpatient visit) with a SARS-Cov-2 test within a 30-day window were considered a single ARI episode from September 25, 2023 through January 31, 2024.

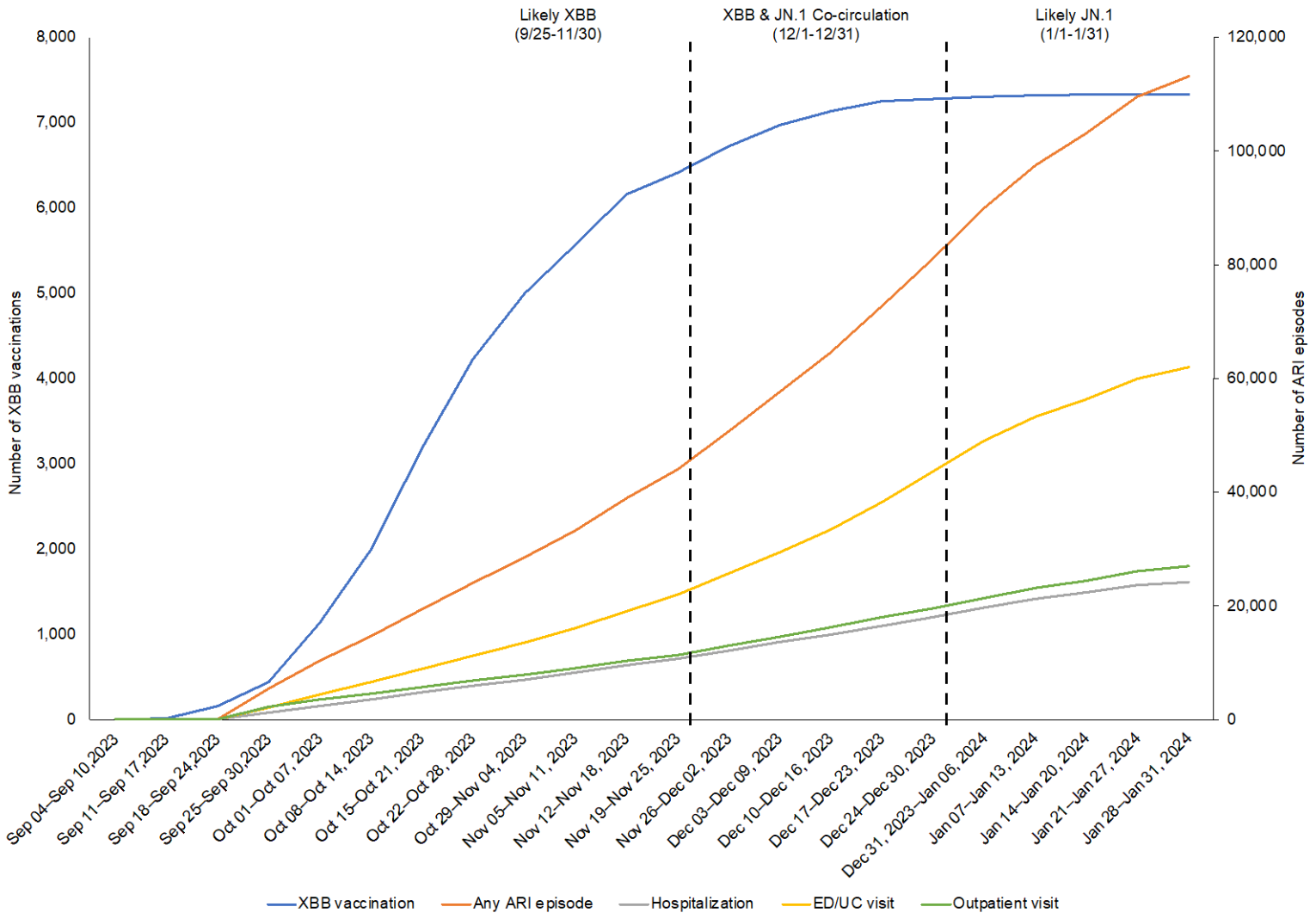
- Likely XBB period defined as September 25, 2023 through November 30, 2023.
- XBB and JN.1 co-circulation period defined as December 1, 2023 through December 31, 2023.
- Likely JN.1 period defined as January 1, 2024 through January 31, 2024.

ARI= acute respiratory infection; ED/UC= emergency department/urgent care;

* The encounter at the highest level of care (i.e., hospitalization > ED/UC visit > outpatient visit) was selected for inclusion.

** Covariates assessed in the year prior for each ARI episode.

Supplemental Figure 2. Cumulative frequency of BNT162b2 XBB vaccination and ARI episodes over time by study time period



ARI= acute respiratory infection; ED/UC= emergency department/urgent care