Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Thompson MG, Stenehjem E, Grannis S, et al. Effectiveness of Covid-19 vaccines in ambulatory and inpatient care settings. N Engl J Med. DOI: 10.1056/NEJMoa2110362

SUPPLEMENTAL APPENDIX

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Section S1. Supplemental Tables Referenced in Manuscript

Table S1. Composition of site-regions and circulation of SARS-CoV-2 Variants of Concern through June 2021 by VISION Network Partners

VISION Partner	Composition of Site-Regions	SARS-CoV-2 Variants of Concern *
Columbia University (CUIMC)	Region 1: Bronx County, Kings County, New York County, Queens County, Richmond County	In March, over a quarter (28%) of viruses identified were B.1.1.7. This percentage increased to 48% by the end of April, 57% by the end of May, but fell to 40% by mid-June. P1 viruses increased from 0.1% at the end of March to <10% by mid-June. B.1.351, B.1.427 and B.1.429 viruses have circulated at very low levels (<5%) from March to June. B.1.617.2 viruses increased from 1.7% by the end of May to 19% by mid-June.
HealthPartners (HP)	Region 1: Hennepin and Ramsey counties; Region 2: Polk, St. Croix and Washington, Mcleod and Renville counties	In March, over half (55%) of viruses identified were B.1.1.7. This percentage increased to 75% by the end of April, 81% by the end of May, and decreased to 73% by mid-June. P1 viruses increased from 0.3% at the end of March to <10% by mid-June. B.1.351, B.1.427 and B.1.429 viruses have circulated at very low levels (<5%) from March to June. B.1.617.2 viruses increased from 0.6% by the end of May to 9% by mid-June.
Intermountain Healthcare (IH)	Region 1: Box Elder county and Cache counties; Region 2: Davis county; Region 3: Tooele and Salt Lake counties; Region 4: Utah county; Region 5: Summit and Wasatch counties; Region 6: Weber county; Region 7: Sanpete, Sevier and Millard counties; Region 8: Garfield, Iron and Washington counties.	As of July 13, 2021, CDC has insufficient genomic surveillance data for the specified time interval for the state of Utah.
Kaiser Permanente Northern California (KPNC)	Region 1: Fresno county; Region 2: Stanislaus county; Region 3: Placer and Sacramento counties; Region 4: Alameda, Contra Costa, Marin, San Francisco, and San Mateo counties; Region 5: Santa Clara county; Region 6: Sonoma county; Region 7: San Joaquin county; Region 8: Solano county	In March, 16% of viruses identified were B.1.1.7. This percentage increased to 45% by the end of April, 58% by the end of May, and decreased to 39% by mid-June. P1 viruses increased from 1.6% at the end of March to 13% by mid-June. While B.1.427 and B.1.429 viruses were identified in 54% of all viruses by the end of March, this percentage decreased to 5% by the end of May. B.1.351 viruses have circulated at very low levels (<5%) from March to June. B.1.617.2 viruses increased from 3.4% by the end of May to 31% by mid-June.
Kaiser Permanente Northwest (KPNW)	Region 1: Multnomah, Washington, Clackamas, Clatsop, and Yamhill counties; Region 2: King, Chelan, Clark, Pacific, Spokane and Cowlitz counties; Region 3: Benton, Deschutes, Harney, Lane, Linn, Marion, Polk, Umatilla, and Wasco counties	CDC had insufficient genomic surveillance data for the period ending March 25 and April 10. By the end of April, 39% of viruses identified were B.1.1.7. This percentage increased to 49% by the end of May and increased to 54% by mid-June. P1 viruses increased from 4% at the end of April to 24% by mid-June. While B.1.427 and B.1.429 viruses were identified in 25% of all viruses by the end of April, this percentage decreased to 10% by the end of May. B.1.351 viruses have circulated at very low levels (<5%) from March to June. B.1.617.2 viruses increased slightly from 0.2% by the end of May to 3% by mid-June.

Regenstrief Institute (RG)	Region 1: Jasper, Lake, La Porte, Newton, Porter; Region 2: Elkhart, Fulton, Kosciusko, Marshall, Pulaski, St. Joseph, Starke; Region 3: Adams, Allen, DeKalb, Huntington, Lagrange, Miami, Noble, Steuben, Wabash, Wells, Whitley; Region 4: Benton, Carroll, Cass, Clinton, Fountain, Tippecanoe, Montgomery, Warren, White; Region 5: Boone, Johnson, Hamilton, Hancock, Hendricks, Marion, Morgan, Shelby; Region 6: Blackford, Delaware, Fayette, Grant, Henry, Howard, Jay, Madison, Randolph, Rush, Tipton, Union, Wayne; Region 7: Clay, Greene, Owen, Parke, Putnam, Sullivan, Vermillion, Vigo; Region 8: Bartholomew, Brown, Jackson, Lawrence, Monroe, Orange, Washington; Region 9: Clark, Dearborn, Decatur, Floyd, Franklin, Harrison, Jefferson, Jennings, Ohio, Ripley, Scott, Switzerland; Region 10: Crawford, Daviess, Dubois, Gibson, Knox, Martin, Spencer, Perry, Pike, Posey, Vanderburgh, Warrick; Region 11: all encounters missing county information	In March, almost a quarter (24%) of viruses identified were B.1.1.7. This percentage increased to 65% by the end of April and 73% by the beginning of June. P1 viruses increased from 0.6% at the end of March to 12% by early June. B.1.351, B.1.427 and B.1.429 viruses have circulated at very low levels (<10%) from March to June. B.1.617.2 viruses increased from 2.3% by the end of May to 8% by early June. CDC had insufficient genomic surveillance data for the period ending June 19.
University of Colorado (UCO)	Region 1: Adams, Arapahoe, Douglas, Boulder, Denver, Broomfield and Jefferson counties; Region 2: Larimer, Weld and Routt counties; Region 3: El Paso and Teller counties	In March, over a quarter (29%) of viruses identified were B.1.1.7. This percentage increased to 60% by the end of April, 80% by the end of May, and decreased to 52% by mid-June. While B.1.427 and B.1.429 viruses were identified in 28% of all viruses by the end of March, this percentage dropped to 2% by the end of May. B.1.351, and P1 viruses have circulated at very low levels (<5%) from March to June. B.1.617.2 viruses increased from 4.3% by the end of May to 37% by mid-June.

* As of July 13, 2021, there are four Variants of Concern circulating in the United States (B.1.1.7, B.1.351, B.1.617.2, and P.1). B.1.427 and B.1.429 had previously been designated variants of concern but have been reclassified as variants of interest as both have conclusively demonstrated to no longer pose a major added risk to global health compared to other circulating SARS-CoV-2 variants. Proportions are based on CDC sequence data (NS3 + CDC-funded contract sequencing) collected over a 4-week period for states with at least 300 sequences. Proportions are calculated using empirical (unweighted) data, which are subject to change over time. Sequences are assigned to a jurisdiction based on where the specimen was collected. Proportions of variants do not represent the total number that may be circulating in the United States and may not match cases reported by states, territories, tribe and local officials. Data available at CDC COVID Data Tracker (https://covid.cdc.gov/covid-data-tracker/#variant-proportions). Site accessed on April 20, May 4, May 18, June 1, June 15, June 29 and July 13, 2021.

Table S2. Acute illness categories and related International Classification of Diseases, 9th and 10th Revision (ICD) discharge codes

Disease Condition	ICD-10 Codes	ICD-9 Codes
COVID-19		
COVID-19, virus identified	U07.1, U07.2	N/A
COVID-19, virus not identified	U07.1, U07.2	N/A
Coronavirus infection, unspecified	B34.2	N/A
COVID-19 Pneumonia		
Pneumonia due to SARS-associated coronavirus	J12.81	N/A
Pneumonia due to coronavirus disease 2019	J12.82	N/A
Influenza Pneumonia		
Influenza due to identified novel influenza A virus with pneumonia	J09.X1	488.81
Influenza due to other identified influenza virus with pneumonia	J10.0	N/A
Influenza due to other identified influenza virus with unspecified type of pneumonia	J10.00	487
Influenza due to other identified influenza virus with the same other identified influenza virus pneumonia	J10.01	487
Influenza due to other identified influenza virus with other specified pneumonia	J10.08	487.0, 488.11
Influenza due to unidentified influenza virus with pneumonia	J11.0	N/A
Influenza due to unidentified influenza virus with unspecified type of pneumonia	J11.00	487
Influenza due to unidentified influenza virus with specified pneumonia	J11.08	487
Influenza with pneumonia	N/A	487*
Other Viral Pneumonia	J12*	480*
Bacterial and Other Pneumonia		
Streptococcus pneumoniae pneumonia	J13	481
Hemophilus influenzae pneumonia	J14	482.2
Other bacterial pneumonia	J15*	482*
Pneumonia due to other specified organism	J16*	483*
Pneumonia in infectious diseases classified elsewhere	J17	484*
Pneumonia, unspecified organism	J18*	486

Influenza Disease	J09*, J10.1, J10.2, J10.8*, J11.1, J11.2, J11.8*	488*
Acute respiratory distress syndrome	J80	518.82
COPD with acute exacerbation	J44.1	491.21
Asthma acute exacerbation	J45.*	493.*
Respiratory failure		
Acute respiratory failure	J96.0*	518.81
Acute and chronic respiratory failure	J96.2*	518.84
Respiratory arrest	R09.2	799.1
Other acute lower respiratory tract infections		
Acute bronchitis	J20*	466
Acute bronchiolitis	J21*	466.1*
Unspecified acute lower respiratory infection	J22	519.8
Bronchitis, not specified as acute or chronic	J40	490
Other chronic obstructive pulmonary disease	J44	N/A
COPD with acute lower respiratory infection	J44.0	491.22
Chronic obstructive pulmonary disease, unspecified	J44.9	491.20, 496
Simple and mucopurulent chronic bronchitis	J41*	491*
Unspecified chronic bronchitis	J42	491.9
Emphysema	J43*	492*
Bronchiectasis	J47*	494*
Abscess of lung and mediastinum	J85	513
Gangrene and necrosis of lung	J85.0	N/A
Abscess of lung without pneumonia	J85.2	513
Abscess of mediastinum	J85.3	513.1
Abscess of lung with pneumonia	J85.1	513
Pyothorax	J86*	510*
Acute and chronic sinusitis	J01*, J32*	461*,473*
Acute upper respiratory tract infections	J00*, J02*-J06*	460*, 462*-465*
Signs and symptoms of acute respiratory illness		
Hemoptysis	R04.2	786.3
Cough	R05	786.2
Dyspnea unspecified	R06.00	786.09
Shortness of breath	R06.02	786.05
Acute respiratory distress	R06.03	N/A

Stridor	R06.1	786.1
Wheezing	R06.2	786.07
Other abnormalities of breathing	R06.8	N/A
Apnea, not elsewhere classified	R06.81	786.03
Tachypnea, NEC	R06.82	786.06
Other abnormalities of breathing/ Other symptoms involving head & neck	R06.89	784.99
Other dyspnea and respiratory abnormality	N/A	786.09
Other symptoms involving respiratory system and chest	N/A	786.9
Chest pain on breathing/ painful respiration	R07.1	786.52
Asphyxia and hypoxemia	R09.0*	N/A
Asphyxia	R09.01	799.01
Hypoxemia	R09.02	799.02
Pleurisy	R09.1	511
Respiratory arrest	R09.2	799.1
Abnormal sputum	R09.3	786.4
Other specified symptoms and signs involving the circulatory and respiratory systems	R09.8*	478.19, 784.91, 786.7
Signs and symptoms of acute febrile illness		
Fever	R50*	N/A
Fever presenting with conditions classified elsewhere	R50.81	780.61
Fever unspecified	R50.9	780.6
Chills (without fever)	R68.83	780.64
Signs and symptoms of acute non-respiratory illness		
Diarrhea	R19.7	787.91
Disturbance of smell and taste	R43*	N/A
Unspecified disturbances of smell and taste	R43.9	781.1, V41.5
Headache	R51*	784
Myalgia	M79.1*	729.1
Sepsis - Symptoms and signs specifically associated with systemic inflammation and infection	R65*	785.52
Other malaise	R53.81	780.79
Other fatigue	R53.83	780.79
Shock, unspecified	R57.9	785.5
Debility unspecified	N/A	799.3
Altered level of consciousness / altered mental status	R41.82, R40*	780.97, 780.0*
Weakness	R53.1	780.79

Nausea and Vomiting	R11.*	787*
Rash and other nonspecific skin eruption	R21.*	782.1
Abdominal pain	R10*	789*

* Includes all sub-codes

Table S3. Inclusion and exclusion for hospitalizations analytic sample

Panel A – Inclusion and Exclusion Table

	Hospital analytic sample							
	Combined Sample	**CUIMC**	**HP**	**IH**	**KPNC**	**KPNW**	**RG**	**UCO**
Hospitalizations among adults age 50 years and older with CLI diagnosis	103,199	5,370	2,090	11,846	31,444	5,379	37,472	9,598
EXCLUDE adults hospitalized prior to age-specific inclusion dates	<37,614>	<1,619>	<802>	<4,028>	<14,811>	<2,902>	<10,478>	<2,974>
Hospitalizations among vaccine eligible adults	65,585	3,751	1,288	7,818	16,633	2,477	26,994	6,624
EXCLUDE if days from discharge are less than lag time for vaccine record update	<1,185>	<0>	<0>	<261>	<0>	<0>	<872>	<52>
Hospitalizations among vaccine eligible adults with updated vaccine records	64,400	3,751	1,288	7,557	16,633	2,477	26,122	6,572
EXCLUDE repeat admissions within 30 days now combined into single events	<6,607>	<448>	<136>	<569>	<2,216>	<236>	<2,358>	<644>
Unique adult hospitalizations among vaccine eligible adults with updated vaccine records	57,793	3,303	1,152	6,988	14,417	2,241	23,764	5,928
EXCLUDE no molecular SARS-CoV-2 testing <14 days to 72-hours after admission	<14,772>	<35>	<61>	<2,820>	<593>	<160>	<10,642>	<461>
Hospitalizations among vaccine eligible with updated records and clinically tested	43,021	3,268	1,091	4,168	13,824	2,081	13,122	5,467
EXCLUDE patients receiving dose-1 <14 days prior to index hospitalization date	<1,872>	<142>	<102>	<258>	<403>	<129>	<685>	<153>
Analytic sample of hospitalizations including all COVID-19 vaccines	41,552	3,126	989	3,910	13,824	1,952	12,437	5,314

Foot notes:

CUIMC: Columbia University Irving Medical Center
HP: HealthPartners
IH: Intermountain Healthcare
KPNC: Kaiser Permanente Northern California
KPNW: Kaiser Permanente Northwest
RG: Regenstrief Institute
UCO: University of Colorado

Panel B. Flowcharts for inclusion and exclusion into samples of COVID-19-associated hospitalizations

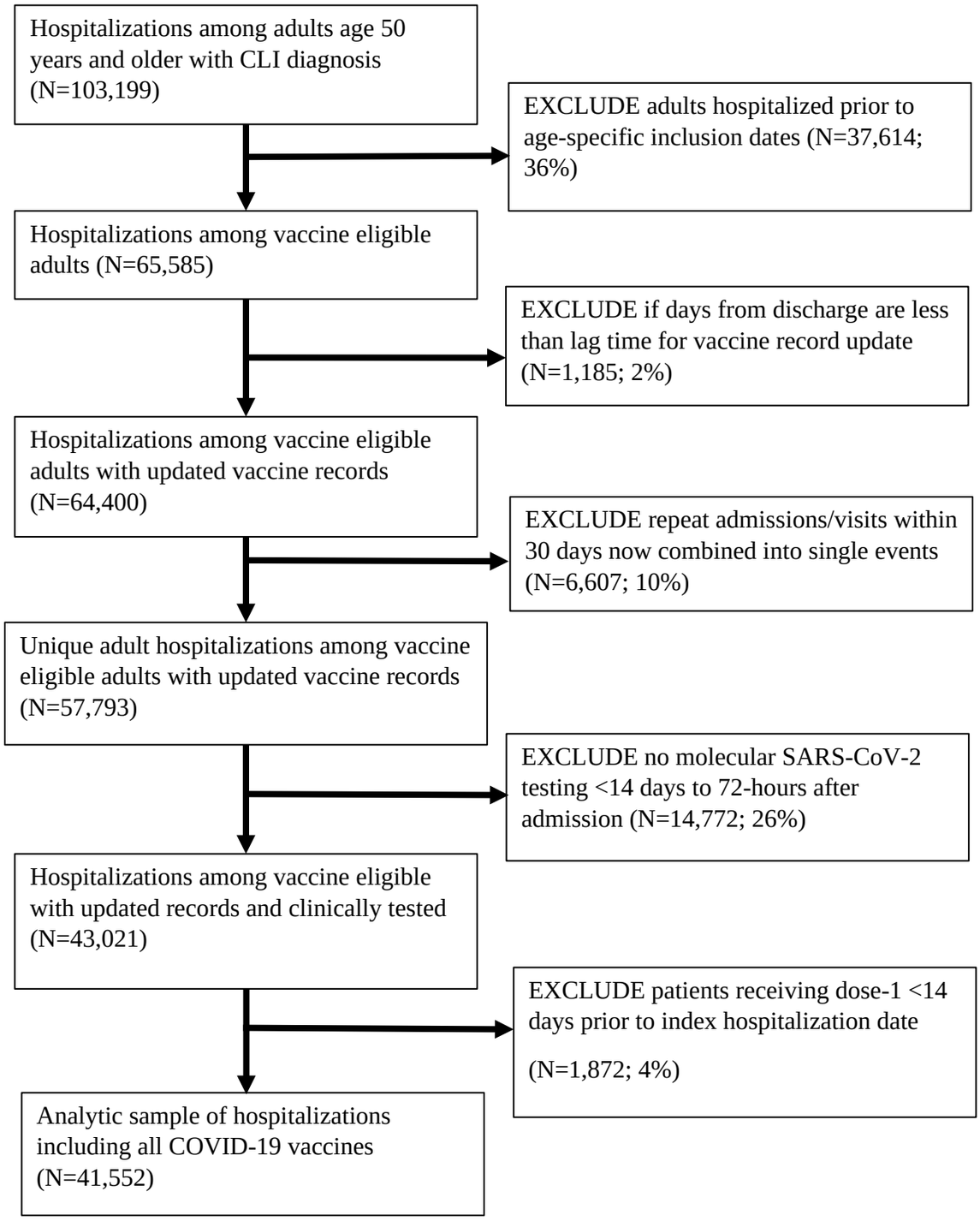


Table S4. Median Days (Lower and Upper quartiles [Q1-Q3]) from vaccine eligibility to index date among unvaccinated and from most recent vaccine dose to index date among vaccinated adults aged ≥50 years for analytic sample of hospitalizations and emergency department and urgent care (ED/UC) encounters

	Days from Vaccine Eligibility by Patient's Age to Index Date among Unvaccinated, Median (Q1-Q3)			Days from Most Recent Vaccine Dose to Index Date among Vaccinated, Median (Q1-Q3)		
	All	**Negatives**	**Positives**	**All**	**Negatives**	**Positives**
Hospitalizations						
Unvaccinated	39 (16-70)	40 (16-71)	38 (14-67)			
Either mRNA vaccine						
Partially 1-Dose Vaccinated				24 (18-39)	25 (19-41)	20 (16-27)
Partially 2-Dose Vaccinated				8 (4-11)	8 (4-11)	6 (3-10)
Full 2-dose mRNA Vaccinated				53 (33-75)	53 (33-75)	56 (36-78)
BioNTech-Pfizer						
Partially 1-Dose Vaccinated				21 (17-39)	22 (18-43)	19 (16-26)
Partially 2-Dose Vaccinated				8 (4-11)	8 (4-11)	6 (4-10)
Full 2-dose Vaccinated				53 (33-76)	53 (33-75)	57 (37-82)
Moderna						
Partially 1-Dose Vaccinated				26 (20-39)	26 (20-40)	21 (16-28)
Partially 2-Dose Vaccinated				7 (4-11)	7 (4-11)	6 (2-9)
Full 2-dose Vaccinated				52 (33-75)	52 (33-75)	53 (34-73)
Johnson & Johnson						
Full 1-dose Vaccinated				42 (28-61)	42 (28-61)	38 (25-54)
ICU Admissions						
Either mRNA vaccine						
Partially 1-Dose Vaccinated				23 (18-37)	24 (19-38)	20 (17-25)
Partially 2-Dose Vaccinated				8 (4-11)	8 (5-11)	4 (3-8)
Full 2-dose mRNA Vaccinated				52 (34-73)	52 (34-73)	61 (36-89)
ED/UC						
Unvaccinated	39 (15-70)	38 (15-70)	40 (14-70)			

Either mRNA vaccine			
Partially 1-Dose Vaccinated	22 (18-29)	23 (18-30)	19 (16-24)
Partially 2-Dose Vaccinated	7 (4-10)	7 (4-10)	6 (4-8)
Full 2-dose mRNA Vaccinated	50 (31-73)	49 (31-73)	64 (39-88)
BioNTech-Pfizer			
Partially 1-Dose Vaccinated	20 (17-27)	21 (17-28)	19 (16-23)
Partially 2-Dose Vaccinated	8 (4-11)	8 (4-11)	6 (2-8)
Full 2-dose Vaccinated	50 (31-74)	50 (31-73)	70 (42-97)
Moderna			
Partially 1-Dose Vaccinated	24 (19-30)	24 (19-30)	19 (16-27)
Partially 2-Dose Vaccinated	7 (3-10)	7 (3-10)	5 (4-8)
Full 2-dose Vaccinated	49 (31-72)	49 (31-72)	52 (31-65)
Johnson & Johnson			
Full 1-dose Vaccinated	44 (27-64)	44 (27-64)	42 (26-64)

Table S5. Inclusion and exclusion for ED/UC analytic sample

Panel A. Inclusion and Exclusion Table

	Emergency department (ED) and urgent care (UC) medical events analytic sample			
	Combined Sample	**IH**	**KPNW**	**RG**
Encounters/events among adults age 50 years and older with CLI diagnosis	121,709	47,877	24,817	49,015
EXCLUDE adults with encounters/events prior to age-specific inclusion dates	<44,334>	<16,543>	<12,277>	<15,514>
Encounters/events among vaccine eligible adults	77,375	31,334	12,540	33,501
EXCLUDE if days from discharge are less than lag time for vaccine record update	<1,155>	<0>	<321>	<834>
Encounters/events among vaccine eligible adults with updated vaccine records	76,220	31,334	12,219	32,667
EXCLUDE repeat encounters within 24 hours now combined into single events	<489>	<332>	<69>	<88>
Unique adult encounters/events among vaccine eligible adults with updated vaccine records	75,731	31,002	12,150	32,579
EXCLUDE no molecular SARS-CoV-2 testing <14 days to 72-hours after visit	<52,859>	<21,385>	<7,191>	<24,283>
Encounters/events among vaccine eligible with updated records and clinically tested	22,872	9,617	4,959	8,296
EXCLUDE patients receiving dose-1 <14 days prior to index visit date	<1,350>	<624>	<277>	<449>
Analytic sample of or encounters/events including all COVID-19 vaccines	21,522	8,993	4,682	7,847

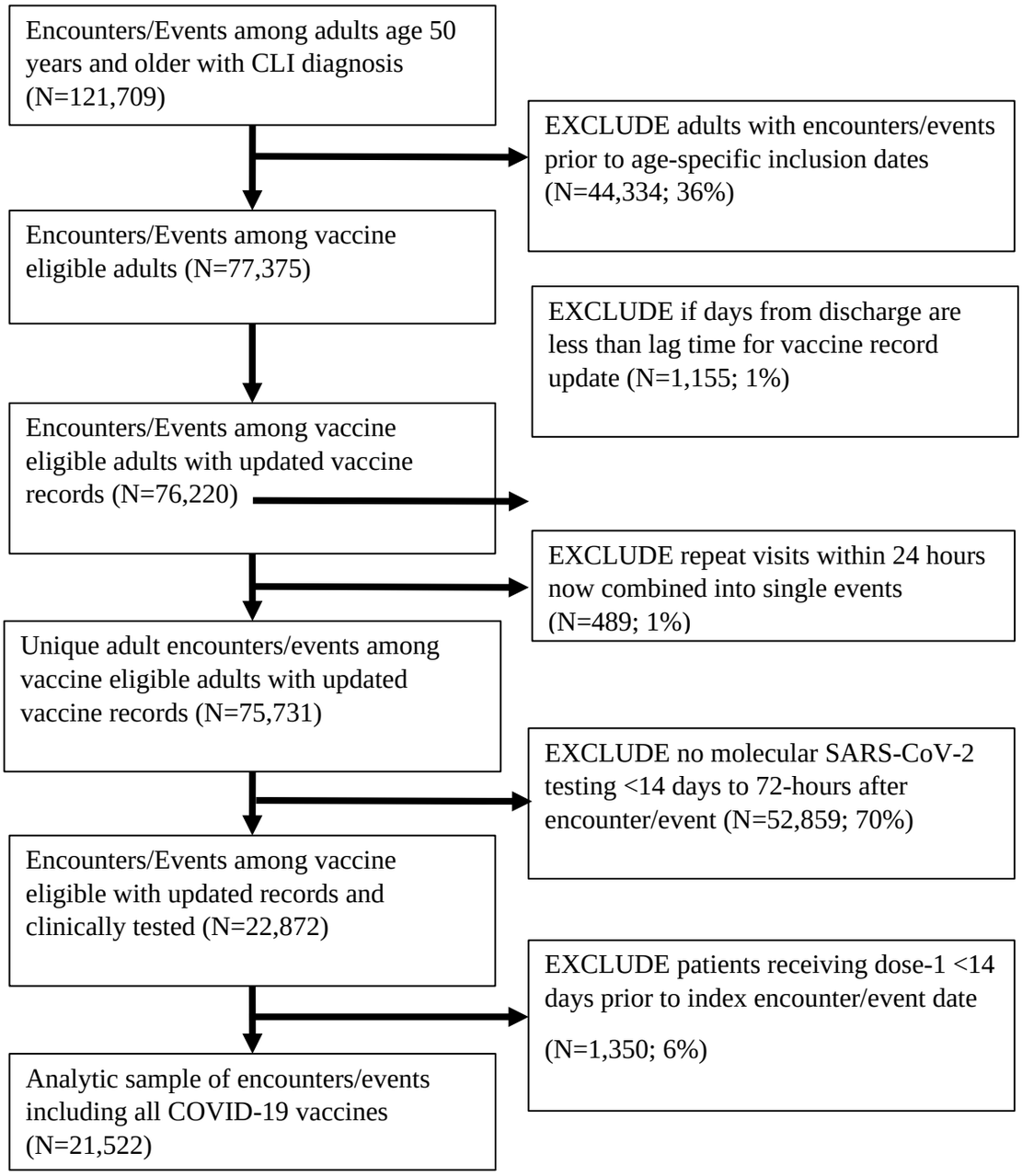
Foot notes:

IH: Intermountain Healthcare

KPNW: Kaiser Permanente Northwest

RG: Regenstrief Institute

Panel B. Flowcharts for inclusion and exclusion into samples of COVID-19-associated emergency department and urgent care (ED/UC) encounters



Tables S6-S11: Characteristics by Site

Table S6. Characteristics of adults with medically attended COVID-19-like illness and the percent with laboratory-confirmed SARS-CoV-2 infection and percent unvaccinated, partially vaccinated with messenger RNA (mRNA) vaccines, or fully vaccinated with mRNA or Ad26.COV2.S vaccines, COLUMBIA UNIVERSITY

	Total Medical Events	SARS-CoV-2 Negatives	SARS-CoV-2 Positives		Unvaccinated	Partially mRNA Vaccinated (1 dose)[1]	Partially mRNA Vaccinated (2 doses)[2]	Fully mRNA Vaccinated[3]	Fully Ad26.COV2.S Vaccinated[3]	
	N (Col. %)	N (Row %)	N (Row %)	SMD	N (Row %)	N (Row %)	N (Row %)	N (Row %)	N (Row %)	SMD[4]
A. Hospitalizations										
All hospitalizations	3126 (100)	2458 (79)	668 (21)		2181 (70)	216 (7)	103 (3)	588 (19)	38 (1)	
Month of hospitalization index date[5]				0.94						0.56
January	203 (6)	109 (54)	94 (46)		196 (97)	5 (2)	1 (0)	1 (0)	0 (0)	
February	593 (19)	359 (61)	234 (39)		499 (84)	50 (8)	33 (6)	11 (2)	0 (0)	
March	634 (20)	468 (74)	166 (26)		424 (67)	56 (9)	35 (6)	118 (19)	1 (0)	
April	776 (25)	651 (84)	125 (16)		506 (65)	49 (6)	26 (3)	185 (24)	10 (1)	
May	753 (24)	708 (94)	45 (6)		458 (61)	46 (6)	8 (1)	215 (29)	26 (3)	
June	167 (5)	163 (98)	4 (2)		98 (59)	10 (6)	0 (0)	58 (35)	1 (1)	
Site-regions										
Site-region 1	3126 (100)	2458 (79)	668 (21)		2181 (70)	216 (7)	103 (3)	588 (19)	38 (1)	
Age groups				0.31						0.08
50-64 years	573 (18)	507 (88)	66 (12)		415 (72)	44 (8)	13 (2)	89 (16)	12 (2)	
65-74 years	1010 (32)	786 (78)	224 (22)		721 (71)	59 (6)	32 (3)	192 (19)	6 (1)	
75-84 years	932 (30)	701 (75)	231 (25)		631 (68)	67 (7)	32 (3)	189 (20)	13 (1)	
≥85 years	611 (20)	464 (76)	147 (24)		414 (68)	46 (8)	26 (4)	118 (19)	7 (1)	
Race (regardless of ethnicity)				0.29						0.22
White	869 (28)	719 (83)	150 (17)		540 (62)	66 (8)	40 (5)	211 (24)	12 (1)	
Black	659 (21)	555 (84)	104 (16)		484 (73)	50 (8)	14 (2)	100 (15)	11 (2)	
Other[6]	29 (1)	22 (76)	7 (24)		17 (59)	0 (0)	4 (14)	8 (28)	0 (0)	
Unknown	1569 (50)	1162 (74)	407 (26)		1140 (73)	100 (6)	45 (3)	269 (17)	15 (1)	
Ethnicity (regardless of race)				0.26						0.15
Hispanic	1430 (46)	1067 (75)	363 (25)		964 (67)	104 (7)	51 (4)	299 (21)	12 (1)	
Non-Hispanic	1182 (38)	993 (84)	189 (16)		819 (69)	82 (7)	37 (3)	222 (19)	22 (2)	
Unknown	514 (16)	398 (77)	116 (23)		398 (77)	30 (6)	15 (3)	67 (13)	4 (1)	

Underlying respiratory condition at discharge				-0.13					0.06
Chronic respiratory condition[7]	2394 (77)	1913 (80)	481 (20)		1654 (69)	173 (7)	85 (4)	453 (19)	29 (1)	
None	732 (23)	545 (74)	187 (26)		527 (72)	43 (6)	18 (2)	135 (18)	9 (1)	
Underlying non-respiratory condition at discharge				-0.06					0.10
Chronic non-respiratory condition[8]	3098 (99)	2439 (79)	659 (21)		2156 (70)	216 (7)	103 (3)	585 (19)	38 (1)	
None	28 (1)	19 (68)	9 (32)		25 (89)	0 (0)	0 (0)	3 (11)	0 (0)	
COVID-19-like illness (CLI) ICD discharge codes				0.78					-0.11
≥1 CLI clinical diagnosis code[9]	2537 (81)	1870 (74)	667 (26)		1798 (71)	176 (7)	82 (3)	451 (18)	30 (1)	
No clinical diagnosis but ≥1 CLI sign or symptom[10]	589 (19)	588 (100)	1 (0)		383 (65)	40 (7)	21 (4)	137 (23)	8 (1)	
CLI diagnosis and placement among discharge codes				0.21					-0.04
CLI is first or primary diagnosis	2414 (77)	1854 (77)	560 (23)		1696 (70)	173 (7)	80 (3)	431 (18)	34 (1)	
CLI is not first or primary diagnosis	712 (23)	604 (85)	108 (15)		485 (68)	43 (6)	23 (3)	157 (22)	4 (1)	
Intensive care unit (ICU) admissions				-0.07					-0.11
Admitted to ICU	506 (16)	411 (81)	95 (19)		379 (75)	33 (7)	11 (2)	73 (14)	10 (2)	
Not in ICU during hospitalization	2620 (84)	2047 (78)	573 (22)		1802 (69)	183 (7)	92 (4)	515 (20)	28 (1)	
COVID-19 Vaccinations				0.62					
Unvaccinated	2181 (70)	1586 (73)	595 (27)		2181 (100)	0 (0)	0 (0)	0 (0)	0 (0)	
BNT162b2 (Pfizer-BioNTech)	671 (21)	609 (91)	62 (9)		0 (0)	140 (21)	79 (12)	452 (67)	0 (0)	
mRNA-1273 (Moderna)	236 (8)	226 (96)	10 (4)		0 (0)	76 (32)	24 (10)	136 (58)	0 (0)	
Ad26.COV2.S (Johnson & Johnson)	38 (1)	37 (97)	1 (3)		0 (0)	0 (0)	0 (0)	0 (0)	38 (100)	

Footnote:

Note: All patients with indeterminate immunization status (receipt of dose-1 of mRNA vaccine 1-13 days prior to index test date) were excluded from table.

Abbreviations: Standard Mean Difference (SMD), COVID-like Illness (CLI), International Classification of Disease (ICD), Intensive Care Unit (ICU), Emergency Department (ED), Urgent Care (UC

[1]Partially vaccinated with 1 dose: patients received dose-1 of mRNA vaccine ≥ 14 days prior to the index text date, had not received dose-2 by the index test date.

[2]Partially vaccinated with 2 doses: patients received dose-1 and dose-2 of mRNA vaccine, dose-2 receipt date 1-13 days prior to index date.

[3]Fully vaccinated: patients received single dose of J&J vaccine, dose-1 and dose-2 of mRNA vaccine, dose-2 of mRNA vaccine ≥ 14 days prior to the index text date.

[4]Standard Mean Difference (SMD) calculation compares unvaccinated to any receipt of vaccine (partial dose-1, partial dose-2 and full vaccination).

[5]Index date for each medical encounter was defined as the date of respiratory specimen collection associated with the most recent positive or negative SARS-CoV-2 test result prior to the medical encounter or the date of the medical encounter if testing only occurred after the admission or encounter date.

[6]Other race include: Asian, Hawaiian or Other Pacific islander, American Indian or Alaskan Native, Other not-listed and multi-race.

[7]Underlying chronic respiratory conditions include: asthma, chronic obstructive pulmonary disease (COPD), other lung disease.

[8]Underlying chronic non-respiratory conditions include: heart failure, ischemic heart disease, hypertension, other heart disease, stroke, other cerebrovascular disease, diabetes (type 1, 2 and due to other specified conditions), other metabolic disease, clinical obesity, clinically underweight, renal disease, liver disease, blood disorder, other immunosuppressive conditions, organ transplant recipient, cancer, dementia, neurological/musculoskeletal disorder or Down's syndrome.

[9]CLI clinical discharge diagnosis codes include: COVID-19 U codes, COVID-19 pneumonia, influenza pneumonia, other viral pneumonia, pneumonia and influenza (bacterial and other) influenza diseases, acute respiratory distress syndrome (ARDS), COPD exacerbation, asthma exacerbation, respiratory failure, other acute lower respiratory tract infection, sinusitis, acute upper respiratory tract infection.

[10]CLI signs and symptoms include: hemoptysis, cough, dyspnea unspecified, chest pain or breathing/painful respiration, asphyxia, hypoxemia, pleurisy, respiratory arrest, abnormal sputum, other specified symptoms and signs involving the circulatory and respiratory systems, fever, chills (without fever), diarrhea, disturbance of taste or smell, headache, myalgia, sepsis, other malaise, other fatigue, shock (unspecified), debility (unspecified), altered level of consciousness /mental state, weakness, nausea and vomiting, rash or other nonspecific skin eruption, abdominal pain

Table S7. Characteristics of adults with medically attended COVID-19-like illness and the percent with laboratory-confirmed SARS-CoV-2 infection and percent unvaccinated, partially vaccinated with messenger RNA (mRNA) vaccines, or fully vaccinated with mRNA or Ad26.COV2.S vaccines, for combined HEALTHPARTNERS and KAISER PERMANENTE NORTHWEST encounters (due to small cell sizes)

	Total Medical Events	SARS-CoV-2 Negatives	SARS-CoV-2 Positives		Unvaccinated	Partially mRNA Vaccinated (1 dose)[1]	Partially mRNA Vaccinated (2 doses)[2]	Fully mRNA Vaccinated[3]	Fully Ad26.COV2.S Vaccinated[3]	
	N (Col. %)	N (Row %)	N (Row %)	SMD	N (Row %)	N (Row %)	N (Row %)	N (Row %)	N (Row %)	SMD[4]
A. Hospitalizations										
All hospitalizations	2941 (100)	2762 (94)	179 (6)		1295 (44)	308 (10)	236 (8)	1041 (35)	61 (2)	
Month of hospitalization index date[5]				0.45						0.48
January	30 (1)	29 (97)	<5		25 (83)	5 (17)	<5	<5	<5	
February	261 (9)	247 (95)	14 (5)		169 (65)	50 (19)	30 (11)	12 (5)	<5	
March	866 (29)	839 (97)	27 (3)		467 (54)	120 (14)	82 (9)	192 (22)	5 (1)	
April	983 (33)	903 (92)	80 (8)		347 (35)	93 (9)	103 (10)	410 (42)	30 (3)	
May	752 (26)	696 (93)	56 (7)		272 (36)	36 (5)	21 (3)	400 (53)	23 (3)	
June	49 (2)	48 (98)	<5		15 (31)	<5	<5	27 (55)	<5	
Site-regions				0.25						0.22
HealthPartners site-region 1	973 (33)	916 (94)	57 (6)		381 (39)	93 (10)	103 (11)	388 (40)	8 (1)	
HealthPartners site-region 2	16 (1)	12 (75)	<5		8 (50)	5 (31)	<5	<5	<5	
Kaiser Permanente Northwest site-region 1	1376 (47)	1301 (95)	75 (5)		624 (45)	159 (12)	92 (7)	455 (33)	46 (3)	
Kaiser Permanente Northwest site-region 2	394 (13)	362 (92)	32 (8)		204 (52)	36 (9)	20 (5)	128 (32)	6 (2)	
Kaiser Permanente Northwest site-region 3	182 (6)	171 (94)	11 (6)		78 (43)	15 (8)	20 (11)	68 (37)	<5	
Age groups				0.51						0.30
50-64 years	455 (15)	396 (87)	59 (13)		270 (59)	29 (6)	28 (6)	121 (27)	7 (2)	
65-74 years	901 (31)	844 (94)	57 (6)		402 (45)	96 (11)	77 (9)	302 (34)	24 (3)	
75-84 years	985 (33)	943 (96)	42 (4)		390 (40)	116 (12)	83 (8)	375 (38)	21 (2)	
≥85 years	600 (20)	579 (97)	21 (4)		233 (39)	67 (11)	48 (8)	243 (41)	9 (2)	
Race (regardless of ethnicity)				0.35						0.22
White	2519 (86)	2380 (94)	139 (6)		1077 (43)	276 (11)	193 (8)	915 (36)	58 (2)	
Black	139 (5)	119 (86)	20 (14)		78 (56)	11 (8)	7 (5)	42 (30)	<5	
Other[6]	207 (7)	199 (96)	8 (4)		87 (42)	18 (9)	31 (15)	69 (33)	<5	
Unknown	76 (3)	64 (84)	12 (16)		53 (70)	<5	5 (7)	15 (20)	<5	
Ethnicity (regardless of race)				0.21						0.16
Hispanic	76 (3)	66 (87)	10 (13)		40 (53)	6 (8)	12 (16)	17 (22)	<5	
Non-Hispanic	2821 (96)	2656 (94)	165 (6)		1221 (43)	301 (11)	224 (8)	1015 (36)	60 (2)	

Unknown	44 (1)	40 (91)	<5		34 (77)	<5	<5	9 (20)	<5	
Underlying respiratory condition at discharge				0.39						-0.11
Chronic respiratory condition[7]	1813 (62)	1673 (92)	140 (8)		838 (46)	186 (10)	129 (7)	629 (35)	31 (2)	
None	1128 (38)	1089 (97)	39 (3)		457 (41)	122 (11)	107 (9)	412 (37)	30 (3)	
Underlying non-respiratory condition at discharge				-0.13						0.08
Chronic non-respiratory condition[8]	2896 (98)	2723 (94)	173 (6)		1268 (44)	304 (10)	234 (8)	1029 (36)	61 (2)	
None	45 (2)	39 (87)	6 (13)		27 (60)	<5	<5	12 (27)	<5	
COVID-19-like illness (CLI) ICD discharge codes				1.11						-0.14
≥1 CLI clinical diagnosis code[9]	1790 (61)	1614 (90)	176 (10)		836 (47)	188 (11)	128 (7)	603 (34)	35 (2)	
No clinical diagnosis but ≥1 CLI sign or symptom[10]	1151 (39)	1148 (100)	<5		459 (40)	120 (10)	108 (9)	438 (38)	26 (2)	
CLI diagnosis and placement among discharge codes				1.69						-0.24
CLI is first or primary diagnosis	382 (13)	252 (66)	130 (34)		227 (59)	45 (12)	22 (6)	79 (21)	9 (2)	
CLI is not first or primary diagnosis	2559 (87)	2510 (98)	49 (2)		1068 (42)	263 (10)	214 (8)	962 (38)	52 (2)	
Intensive care unit (ICU) admissions				0.02						-0.15
Admitted to ICU	500 (17)	468 (94)	32 (6)		262 (52)	47 (9)	42 (8)	146 (29)	<5	
Not in ICU during hospitalization	2441 (83)	2294 (94)	147 (6)		1033 (42)	261 (11)	194 (8)	895 (37)	58 (2)	
COVID-19 Vaccinations				0.88						
Unvaccinated	1295 (44)	1150 (89)	145 (11)		1295 (100)	0 (0)	0 (0)	0 (0)	0 (0)	
BNT162b2 (Pfizer-BioNTech)	1015 (35)	995 (98)	20 (2)		0 (0)	179 (18)	161 (16)	675 (67)	0 (0)	
mRNA-1273 (Moderna)	570 (19)	558 (98)	12 (2)		0 (0)	129 (23)	75 (13)	366 (64)	0 (0)	
Ad26.COV2.S (Johnson & Johnson)	61 (2)	59 (97)	<5		0 (0)	0 (0)	0 (0)	0 (0)	61 (100)	
B. Emergency Department (ED) and Urgent Care (UC) Visits										
All ED and UC Visits	4682 (100)	4277 (91)	405 (9)		2100 (45)	440 (9)	327 (7)	1702 (36)	113 (2)	
By medical event setting				0.15						0.15
ED visits	3180 (68)	2932 (92)	248 (8)		1507 (47)	299 (9)	223 (7)	1085 (34)	66 (2)	
UC visits	1502 (32)	1345 (90)	157 (10)		593 (39)	141 (9)	104 (7)	617 (41)	47 (3)	
Month of ED/UC event index date[5]				0.53						0.61
January	19 (0)	15 (79)	<5		18 (95)	<5	<5	<5	<5	
February	373 (8)	345 (92)	28 (8)		313 (84)	30 (8)	14 (4)	16 (4)	<5	
March	860 (18)	838 (97)	22 (3)		489 (57)	149 (17)	94 (11)	118 (14)	10 (1)	

April	1239 (26)	1134 (92)	105 (8)		471 (38)	128 (10)	138 (11)	471 (38)	31 (3)	
May	1814 (39)	1600 (88)	214 (12)		684 (38)	111 (6)	71 (4)	894 (49)	54 (3)	
June	377 (8)	345 (92)	32 (8)		125 (33)	21 (6)	10 (3)	203 (54)	18 (5)	
Site-regions				0.17						0.12
Kaiser Permanente Northwest site-region 1	2197 (47)	2004 (91)	193 (9)		915 (42)	232 (11)	147 (7)	828 (38)	75 (3)	
Kaiser Permanente Northwest site-region 2	1939 (41)	1794 (93)	145 (7)		916 (47)	155 (8)	144 (7)	697 (36)	27 (1)	
Kaiser Permanente Northwest site-region 3	546 (12)	479 (88)	67 (12)		269 (49)	53 (10)	36 (7)	177 (32)	11 (2)	
Age groups				0.52						0.18
50-64 years	959 (20)	795 (83)	164 (17)		487 (51)	83 (9)	64 (7)	300 (31)	25 (3)	
65-74 years	1651 (35)	1517 (92)	134 (8)		768 (47)	152 (9)	116 (7)	571 (35)	44 (3)	
75-84 years	1431 (31)	1357 (95)	74 (5)		564 (39)	143 (10)	111 (8)	574 (40)	39 (3)	
≥85 years	641 (14)	608 (95)	33 (5)		281 (44)	62 (10)	36 (6)	257 (40)	5 (1)	
Race (regardless of ethnicity)				0.29						0.12
White	3991 (85)	3682 (92)	309 (8)		1755 (44)	363 (9)	284 (7)	1490 (37)	99 (2)	
Black	145 (3)	121 (83)	24 (17)		80 (55)	16 (11)	<5	46 (32)	<5	
Other[6]	319 (7)	288 (90)	31 (10)		137 (43)	39 (12)	29 (9)	104 (33)	10 (3)	
Unknown	227 (5)	186 (82)	41 (18)		128 (56)	22 (10)	12 (5)	62 (27)	<5	
Ethnicity (regardless of race)				0.17						0.06
Hispanic	249 (5)	216 (87)	33 (13)		115 (46)	26 (10)	25 (10)	76 (31)	7 (3)	
Non-Hispanic	4337 (93)	3979 (92)	358 (8)		1928 (44)	406 (9)	300 (7)	1597 (37)	106 (2)	
Unknown	96 (2)	82 (85)	14 (15)		57 (59)	8 (8)	<5	29 (30)	<5	
Underlying respiratory condition at discharge				-0.18						-0.05
Chronic respiratory condition[7]	1561 (33)	1456 (93)	105 (7)		730 (47)	160 (10)	113 (7)	521 (33)	37 (2)	
None	3121 (67)	2821 (90)	300 (10)		1370 (44)	280 (9)	214 (7)	1181 (38)	76 (2)	
Underlying non-respiratory condition at discharge				-0.29						-0.08
Chronic non-respiratory condition[8]	3267 (70)	3035 (93)	232 (7)		1509 (46)	318 (10)	233 (7)	1138 (35)	69 (2)	
None	1415 (30)	1242 (88)	173 (12)		591 (42)	122 (9)	94 (7)	564 (40)	44 (3)	
COVID-19-like illness (CLI) ICD discharge codes				0.96						-0.15
≥1 CLI clinical diagnosis code[9]	2066 (44)	1732 (84)	334 (16)		1014 (49)	204 (10)	132 (6)	665 (32)	51 (2)	
No clinical diagnosis but ≥1 CLI sign or symptom[10]	2616 (56)	2545 (97)	71 (3)		1086 (42)	236 (9)	195 (7)	1037 (40)	62 (2)	
CLI diagnosis and placement among discharge codes				0.67						-0.19
CLI is first or primary diagnosis	817 (17)	640 (78)	177 (22)		452 (55)	69 (8)	57 (7)	224 (27)	15 (2)	
CLI is not first or primary diagnosis	3865 (83)	3637 (94)	228 (6)		1648 (43)	371 (10)	270 (7)	1478 (38)	98 (3)	

COVID-19 Vaccinations				1.10				
Unvaccinated	2100 (45)	1746 (83)	354 (17)		2100 (100)	0 (0)	0 (0)	0 (0)	0 (0)
BNT162b2 (Pfizer-BioNTech)	1735 (37)	1696 (98)	39 (2)		0 (0)	266 (15)	237 (14)	1232 (71)	0 (0)
mRNA-1273 (Moderna)	734 (16)	726 (99)	8 (1)		0 (0)	174 (24)	90 (12)	470 (64)	0 (0)
Ad26.COV2.S (Johnson & Johnson)	113 (2)	109 (96)	<5		0 (0)	0 (0)	0 (0)	0 (0)	113 (100)

Note: All patients with indeterminate immunization status (receipt of dose-1 of mRNA vaccine 1-13 days prior to index test date) were excluded from table.

Abbreviations: Standard Mean Difference (SMD), COVID-like Illness (CLI), International Classification of Disease (ICD), Intensive Care Unit (ICU), Emergency Department (ED), Urgent Care (UC)

[1]Partially vaccinated with 1 dose: patients received dose-1 of mRNA vaccine ≥ 14 days prior to the index text date, had not received dose-2 by the index test date.

[2]Partially vaccinated with 2 doses: patients received dose-1 and dose-2 of mRNA vaccine, dose-2 receipt date 1-13 days prior to index date.

[3]Fully vaccinated: patients received single dose of J&J vaccine, dose-1 and dose-2 of mRNA vaccine, dose-2 of mRNA vaccine ≥ 14 days prior to the index text date.

[4]Standard Mean Difference (SMD) calculation compares unvaccinated to any receipt of vaccine (partial dose-1, partial dose-2 and full vaccination).

[5]Index date for each medical encounter was defined as the date of respiratory specimen collection associated with the most recent positive or negative SARS-CoV-2 test result prior to the medical encounter or the date of the medical encounter if testing only occurred after the admission or encounter date.

[6]Other race include Asian, Hawaiian or Other Pacific islander, American Indian or Alaskan Native, Other not-listed and multi-race.

[7]Underlying chronic respiratory conditions include asthma, chronic obstructive pulmonary disease (COPD), other lung disease.

[8]Underlying chronic non-respiratory conditions include heart failure, ischemic heart disease, hypertension, other heart disease, stroke, other cerebrovascular disease, diabetes (type 1, 2 and due to other specified conditions), other metabolic disease, clinical obesity, clinically underweight, renal disease, liver disease, blood disorder, other immunosuppressive conditions, organ transplant recipient, cancer, dementia, neurological/musculoskeletal disorder or Down's syndrome.

[9]CLI clinical discharge diagnosis codes include: COVID-19 U codes, COVID-19 pneumonia, influenza pneumonia, other viral pneumonia, pneumonia and influenza (bacterial and other) influenza diagnoses, acute respiratory distress syndrome (ARDS), COPD exacerbation, asthma exacerbation, respiratory failure, other acute lower respiratory tract infection, sinusitis, acute upper respiratory tract infection.

[10]CLI signs and symptoms include: hemoptysis, cough, dyspnea unspecified, chest pain or breathing/painful respiration, asphyxia, hypoxemia, pleurisy, respiratory arrest, abnormal sputum, other specified symptoms and signs involving the circulatory and respiratory systems, fever, chills (without fever), diarrhea, disturbance of taste or smell, headache, myalgia, sepsis, other malaise, other fatigue, shock (unspecified), debility (unspecified), altered level of consciousness/mental state, weakness, nausea and vomiting, rash or other nonspecific skin eruption, abdominal pain

Table S8. Characteristics of adults with medically attended COVID-19-like illness and the percent with laboratory-confirmed SARS-CoV-2 infection and percent unvaccinated, partially vaccinated with messenger RNA (mRNA) vaccines, or fully vaccinated with mRNA or Ad26.COV2.S vaccines, INTERMOUNTAIN HEALTHCARE

	Total Medical Events	SARS-CoV-2 Negatives	SARS-CoV-2 Positives		Unvaccinated	Partially mRNA Vaccinated (1 dose)[1]	Partially mRNA Vaccinated (2 doses)[2]	Fully mRNA Vaccinated[3]	Fully Ad26.COV2.S Vaccinated[3]	
	N (Col. %)	N (Row %)	N (Row %)	SMD	N (Row %)	N (Row %)	N (Row %)	N (Row %)	N (Row %)	SMD[4]
A. Hospitalizations										
All hospitalizations	3910 (100)	3353 (86)	557 (14)		1917 (49)	392 (10)	278 (7)	1236 (32)	87 (2)	
Month of hospitalization index date[5]				0.25						0.34
February	24 (1)	16 (67)	8 (33)		23 (96)	0 (0)	1 (4)	0 (0)	0 (0)	
March	557 (14)	450 (81)	107 (19)		369 (66)	104 (19)	60 (11)	24 (4)	0 (0)	
April	914 (23)	798 (87)	116 (13)		446 (49)	130 (14)	104 (11)	225 (25)	9 (1)	
May	1062 (27)	932 (88)	130 (12)		480 (45)	81 (8)	81 (8)	393 (37)	27 (3)	
June	965 (25)	832 (86)	133 (14)		437 (45)	57 (6)	29 (3)	409 (42)	33 (3)	
	388 (10)	325 (84)	63 (16)		162 (42)	20 (5)	3 (1)	185 (48)	18 (5)	
Site-regions				0.27						0.20
Site-region 1	248 (6)	219 (88)	29 (12)		133 (54)	19 (8)	16 (6)	71 (29)	9 (4)	
Site-region 2	238 (6)	204 (86)	34 (14)		101 (42)	27 (11)	13 (5)	93 (39)	4 (2)	
Site-region 3	1434 (37)	1253 (87)	181 (13)		654 (46)	147 (10)	95 (7)	510 (36)	28 (2)	
Site-region 4	721 (18)	630 (87)	91 (13)		340 (47)	66 (9)	52 (7)	257 (36)	6 (1)	
Site-region 5	67 (2)	58 (87)	9 (13)		34 (51)	6 (9)	9 (13)	17 (25)	1 (1)	
Site-region 6	479 (12)	411 (86)	68 (14)		245 (51)	51 (11)	38 (8)	133 (28)	12 (3)	
Site-region 7	74 (2)	61 (82)	13 (18)		37 (50)	7 (9)	9 (12)	20 (27)	1 (1)	
Site-region 8	649 (17)	517 (80)	132 (20)		373 (57)	69 (11)	46 (7)	135 (21)	26 (4)	
Age groups				0.27						0.34
50-64 years	1036 (26)	843 (81)	193 (19)		633 (61)	85 (8)	56 (5)	221 (21)	41 (4)	
65-74 years	1184 (30)	1010 (85)	174 (15)		595 (50)	121 (10)	75 (6)	368 (31)	25 (2)	
75-84 years	1135 (29)	996 (88)	139 (12)		484 (43)	130 (11)	96 (8)	411 (36)	14 (1)	
≥85 years	555 (14)	504 (91)	51 (9)		205 (37)	56 (10)	51 (9)	236 (43)	7 (1)	
Race (regardless of ethnicity)				0.18						0.19
White	3608 (92)	3117 (86)	491 (14)		1733 (48)	364 (10)	261 (7)	1174 (33)	76 (2)	
Black	26 (1)	20 (77)	6 (23)		19 (73)	1 (4)	0 (0)	4 (15)	2 (8)	
Other[6]	142 (4)	116 (82)	26 (18)		82 (58)	16 (11)	11 (8)	29 (20)	4 (3)	
Unknown	134 (3)	100 (75)	34 (25)		83 (62)	11 (8)	6 (4)	29 (22)	5 (4)	

Ethnicity (regardless of race)				0.30					0.20
Hispanic	276 (7)	198 (72)	78 (28)		179 (65)	26 (9)	18 (7)	47 (17)	6 (2)
Non-Hispanic	3510 (90)	3059 (87)	451 (13)		1662 (47)	358 (10)	252 (7)	1161 (33)	77 (2)
Unknown	124 (3)	96 (77)	28 (23)		76 (61)	8 (6)	8 (6)	28 (23)	4 (3)
Underlying respiratory condition at discharge				-0.03					0.08
Chronic respiratory condition[7]	2394 (61)	2061 (86)	333 (14)		1135 (47)	241 (10)	168 (7)	791 (33)	59 (2)
None	1516 (39)	1292 (85)	224 (15)		782 (52)	151 (10)	110 (7)	445 (29)	28 (2)
Underlying non-respiratory condition at discharge				-0.22					0.11
Chronic non-respiratory condition[8]	3706 (95)	3205 (86)	501 (14)		1793 (48)	374 (10)	267 (7)	1192 (32)	80 (2)
None	204 (5)	148 (73)	56 (27)		124 (61)	18 (9)	11 (5)	44 (22)	7 (3)
COVID-19-like illness (CLI) ICD discharge codes				1.01					-0.10
≥1 CLI clinical diagnosis code[9]	2725 (70)	2172 (80)	553 (20)		1379 (51)	260 (10)	191 (7)	836 (31)	59 (2)
No clinical diagnosis but ≥1 CLI sign or symptom[10]	1185 (30)	1181 (100)	4 (0)		538 (45)	132 (11)	87 (7)	400 (34)	28 (2)
CLI diagnosis and placement among discharge codes				0.78					-0.10
CLI is first or primary diagnosis	1552 (40)	1157 (75)	395 (25)		807 (52)	144 (9)	108 (7)	460 (30)	33 (2)
CLI is not first or primary diagnosis	2358 (60)	2196 (93)	162 (7)		1110 (47)	248 (11)	170 (7)	776 (33)	54 (2)
Intensive care unit (ICU) admissions				0.14					-0.08
Admitted to ICU	318 (8)	253 (80)	65 (20)		176 (55)	28 (9)	23 (7)	88 (28)	3 (1)
Not in ICU during hospitalization	3592 (92)	3100 (86)	492 (14)		1741 (48)	364 (10)	255 (7)	1148 (32)	84 (2)
COVID-19 Vaccinations				0.97					
Unvaccinated	1917 (49)	1446 (75)	471 (25)		1917 (100)	0 (0)	0 (0)	0 (0)	0 (0)
BNT162b2 (Pfizer-BioNTech)	1068 (27)	1021 (96)	47 (4)		0 (0)	200 (19)	146 (14)	722 (68)	0 (0)
mRNA-1273 (Moderna)	838 (21)	803 (96)	35 (4)		0 (0)	192 (23)	132 (16)	514 (61)	0 (0)
Ad26.COV2.S (Johnson & Johnson)	87 (2)	83 (95)	4 (5)		0 (0)	0 (0)	0 (0)	0 (0)	87 (100)

B. Emergency Department (ED) and Urgent Care (UC) Visits										
All ED and UC Visits	8993 (100)	7600 (85)	1393 (15)		4612 (51)	908 (10)	557 (6)	2700 (30)	216 (2)	
By medical event setting				0.13						-0.03
ED visits	7348 (82)	6272 (85)	1076 (15)		3744 (51)	711 (10)	461 (6)	2252 (31)	180 (2)	
UC visits	1645 (18)	1328 (81)	317 (19)		868 (53)	197 (12)	96 (6)	448 (27)	36 (2)	
Month of ED/UC event index date[5]				0.27						0.32
February	53 (1)	30 (57)	23 (43)		52 (98)	1 (2)	0 (0)	0 (0)	0 (0)	
March	1141 (13)	907 (79)	234 (21)		785 (69)	207 (18)	100 (9)	49 (4)	0 (0)	
April	1944 (22)	1676 (86)	268 (14)		1002 (52)	316 (16)	198 (10)	414 (21)	14 (1)	
May	2558 (28)	2229 (87)	329 (13)		1217 (48)	235 (9)	192 (8)	838 (33)	76 (3)	
June	2173 (24)	1837 (85)	336 (15)		1013 (47)	106 (5)	52 (2)	923 (42)	79 (4)	
	1124 (12)	921 (82)	203 (18)		543 (48)	43 (4)	15 (1)	476 (42)	47 (4)	
Site-regions				0.24						0.16
Site-region 1	605 (7)	522 (86)	83 (14)		278 (46)	55 (9)	35 (6)	225 (37)	12 (2)	
Site-region 2	356 (4)	278 (78)	78 (22)		180 (51)	35 (10)	22 (6)	116 (33)	3 (1)	
Site-region 3	3266 (36)	2864 (88)	402 (12)		1542 (47)	351 (11)	219 (7)	1073 (33)	81 (2)	
Site-region 4	1418 (16)	1166 (82)	252 (18)		721 (51)	129 (9)	80 (6)	472 (33)	16 (1)	
Site-region 5	310 (3)	262 (85)	48 (15)		165 (53)	31 (10)	24 (8)	82 (26)	8 (3)	
Site-region 6	1146 (13)	983 (86)	163 (14)		623 (54)	111 (10)	72 (6)	307 (27)	33 (3)	
Site-region 7	283 (3)	241 (85)	42 (15)		159 (56)	27 (10)	15 (5)	77 (27)	5 (2)	
Site-region 8	1609 (18)	1284 (80)	325 (20)		944 (59)	169 (11)	90 (6)	348 (22)	58 (4)	
Age groups				0.30						0.41
50-64 years	3070 (34)	2468 (80)	602 (20)		1919 (63)	253 (8)	149 (5)	630 (21)	119 (4)	
65-74 years	2654 (30)	2237 (84)	417 (16)		1366 (51)	280 (11)	156 (6)	796 (30)	56 (2)	
75-84 years	2213 (25)	1931 (87)	282 (13)		924 (42)	263 (12)	159 (7)	840 (38)	27 (1)	
≥85 years	1056 (12)	964 (91)	92 (9)		403 (38)	112 (11)	93 (9)	434 (41)	14 (1)	
Race (regardless of ethnicity)				0.12						0.18
White	8227 (91)	6990 (85)	1237 (15)		4132 (50)	833 (10)	521 (6)	2548 (31)	193 (2)	
Black	75 (1)	60 (80)	15 (20)		54 (72)	3 (4)	2 (3)	12 (16)	4 (5)	
Other[6]	366 (4)	300 (82)	66 (18)		216 (59)	45 (12)	20 (5)	78 (21)	7 (2)	
Unknown	325 (4)	250 (77)	75 (23)		210 (65)	27 (8)	14 (4)	62 (19)	12 (4)	
Ethnicity (regardless of race)				0.29						0.19

Hispanic	788 (9)	569 (72)	219 (28)		502 (64)	71 (9)	39 (5)	160 (20)	16 (2)	
Non-Hispanic	7921 (88)	6802 (86)	1119 (14)		3935 (50)	814 (10)	505 (6)	2478 (31)	189 (2)	
Unknown	284 (3)	229 (81)	55 (19)		175 (62)	23 (8)	13 (5)	62 (22)	11 (4)	
Underlying respiratory condition at discharge				-0.14						0.08
Chronic respiratory condition[7]	3998 (44)	3462 (87)	536 (13)		1956 (49)	410 (10)	255 (6)	1271 (32)	106 (3)	
None	4995 (56)	4138 (83)	857 (17)		2656 (53)	498 (10)	302 (6)	1429 (29)	110 (2)	
Underlying non-respiratory condition at discharge				-0.20						0.12
Chronic non-respiratory condition[8]	6673 (74)	5743 (86)	930 (14)		3306 (50)	665 (10)	425 (6)	2124 (32)	153 (2)	
None	2320 (26)	1857 (80)	463 (20)		1306 (56)	243 (10)	132 (6)	576 (25)	63 (3)	
COVID-19-like illness (CLI) ICD discharge codes				0.89						-0.12
≥1 CLI clinical diagnosis code[9]	5534 (62)	4256 (77)	1278 (23)		2969 (54)	521 (9)	319 (6)	1588 (29)	137 (2)	
No clinical diagnosis but ≥1 CLI sign or symptom[10]	3459 (38)	3344 (97)	115 (3)		1643 (47)	387 (11)	238 (7)	1112 (32)	79 (2)	
CLI diagnosis and placement among discharge codes				0.84						-0.18
CLI is first or primary diagnosis	5143 (57)	3927 (76)	1216 (24)		2835 (55)	499 (10)	289 (6)	1385 (27)	135 (3)	
CLI is not first or primary diagnosis	3850 (43)	3673 (95)	177 (5)		1777 (46)	409 (11)	268 (7)	1315 (34)	81 (2)	
COVID-19 Vaccinations				0.96						
Unvaccinated	4612 (51)	3419 (74)	1193 (26)		4612 (100)	0 (0)	0 (0)	0 (0)	0 (0)	
BNT162b2 (Pfizer-BioNTech)	2302 (26)	2186 (95)	116 (5)		0 (0)	422 (18)	307 (13)	1573 (68)	0 (0)	
mRNA-1273 (Moderna)	1863 (21)	1792 (96)	71 (4)		0 (0)	486 (26)	250 (13)	1127 (60)	0 (0)	
Ad26.COV2.S (Johnson & Johnson)	216 (2)	203 (94)	13 (6)		0 (0)	0 (0)	0 (0)	0 (0)	216 (100)	

Note: All patients with indeterminate immunization status (receipt of dose-1 of mRNA vaccine 1-13 days prior to index test date) were excluded from table.

Abbreviations: Standard Mean Difference (SMD), COVID-like Illness (CLI), International Classification of Disease (ICD), Intensive Care Unit (ICU), Emergency Department (ED), Urgent Care (UC)

[1]Partially vaccinated with 1 dose: patients received dose-1 of mRNA vaccine ≥ 14 days prior to the index text date, had not received dose-2 by the index test date.

[2]Partially vaccinated with 2 doses: patients received dose-1 and dose-2 of mRNA vaccine, dose-2 receipt date 1-13 days prior to index date.

[3]Fully vaccinated: patients received single dose of J&J vaccine, dose-1 and dose-2 of mRNA vaccine, dose-2 of mRNA vaccine ≥ 14 days prior to the index text date.

[4]Standard Mean Difference (SMD) calculation compares unvaccinated to any receipt of vaccine (partial dose-1, partial dose-2 and full vaccination).

[5]Index date for each medical encounter was defined as the date of respiratory specimen collection associated with the most recent positive or negative SARS-CoV-2 test result prior to the medical encounter or the date of the medical encounter if testing only occurred after the admission or encounter date.

[6]Other race include Asian, Hawaiian or Other Pacific islander, American Indian or Alaskan Native, Other not-listed and multi-race.

[7]Underlying chronic respiratory conditions include asthma, chronic obstructive pulmonary disease (COPD), other lung disease.

[8]Underlying chronic non-respiratory conditions include heart failure, ischemic heart disease, hypertension, other heart disease, stroke, other cerebrovascular disease, diabetes (type 1, 2 and due to other specified conditions), other metabolic disease, clinical obesity, clinically underweight, renal disease, liver disease, blood disorder, other immunosuppressive conditions, organ transplant recipient, cancer, dementia, neurological/musculoskeletal disorder or Down's syndrome.

[9]CLI clinical discharge diagnosis codes include: COVID-19 U codes, COVID-19 pneumonia, influenza pneumonia, other viral pneumonia, pneumonia and influenza (bacterial and other) influenza diagnoses, acute respiratory distress syndrome (ARDS), COPD exacerbation, asthma exacerbation, respiratory failure, other acute lower respiratory tract infection, sinusitis, acute upper respiratory tract infection.

[10]CLI signs and symptoms include: hemoptysis, cough, dyspnea unspecified, chest pain or breathing/painful respiration, asphyxia, hypoxemia, pleurisy, respiratory arrest, abnormal sputum, other specified symptoms and signs involving the circulatory and respiratory systems, fever, chills (without fever), diarrhea, disturbance of taste or smell, headache, myalgia, sepsis, other malaise, other fatigue, shock (unspecified), debility (unspecified), altered level of consciousness/mental state, weakness, nausea and vomiting, rash or other nonspecific skin eruption, abdominal pain

Table S9. Characteristics of adults with medically attended COVID-19-like illness and the percent with laboratory-confirmed SARS-CoV-2 infection and percent unvaccinated, partially vaccinated with messenger RNA (mRNA) vaccines, or fully vaccinated with mRNA or Ad26.COV2.S vaccines, KAISER PERMANENTE NORTHERN CALIFORNIA

	Total Medical Events		SARS-CoV-2 Negatives		SARS-CoV-2 Positives			Unvaccinated		Partially mRNA Vaccinated (1 dose)[1]		Partially mRNA Vaccinated (2 doses)[2]		Fully mRNAVaccinated[3]		Fully Ad26.COV2.S Vaccinated[3]		
	N	Col. %	N	Row %	N	Row %	SMD	N	Row %	N	Row %	N	Row %	N	Row %	N	Row %	SMD[4]
A. Hospitalizations																		
All hospitalizations	13824	100	13159	95	665	5		3559	26	1021	7	980	7	7874	57	390	3	
Month of hospitalization index date[5]							0.14											0.23
March	2471	18	2352	95	119	5		826	33	375	15	469	19	797	32	4	0	
April	4460	32	4218	95	242	5		1218	27	320	7	348	8	2448	55	126	3	
May	4960	36	4724	95	236	5		1144	23	260	5	143	3	3241	65	172	3	
June	1933	14	1865	96	68	4		371	19	66	3	20	1	1388	72	88	5	
Site-regions							0.47											0.28
Site-region 1	705	5	651	92	54	8		223	32	68	10	49	7	347	49	18	3	
Site-region 2	510	4	453	89	57	11		211	41	41	8	25	5	225	44	8	2	
Site-region 3	3200	23	2981	93	219	7		997	31	255	8	204	6	1683	53	61	2	
Site-region 4	5660	41	5478	97	182	3		1262	22	370	7	432	8	3410	60	186	3	
Site-region 5	1660	12	1605	97	55	3		338	20	117	7	118	7	1023	62	64	4	
Site-region 6	676	5	663	98	13	2		123	18	57	8	47	7	428	63	21	3	
Site-region 7	267	2	243	91	24	9		91	34	19	7	20	7	132	49	5	2	
Site-region 8	1146	8	1085	95	61	5		314	27	94	8	85	7	626	55	27	2	
Age groups							0.45											0.30
50-64 years	2347	17	2118	90	229	10		871	37	183	8	202	9	938	40	153	7	
65-74 years	4288	31	4096	96	192	4		1178	27	377	9	336	8	2302	54	95	2	
75-84 years	4330	31	4181	97	149	3		907	21	280	6	288	7	2768	64	87	2	
≥85 years	2859	21	2764	97	95	3		603	21	181	6	154	5	1866	65	55	2	
Race (regardless of ethnicity)							0.34											0.20
White	8712	63	8374	96	338	4		2083	24	658	8	586	7	5160	59	225	3	
Black	1355	10	1260	93	95	7		493	36	119	9	113	8	581	43	49	4	
Other[6]	2225	16	2128	96	97	4		518	23	134	6	160	7	1342	60	71	3	
Unknown	1532	11	1397	91	135	9		465	30	110	7	121	8	791	52	45	3	
Ethnicity (regardless of race)							0.39											0.25
Hispanic	2070	15	1914	92	156	8		616	30	141	7	159	8	1088	53	66	3	
Non-Hispanic	8532	62	8243	97	289	3		1881	22	616	7	584	7	5253	62	198	2	
Unknown	3222	23	3002	93	220	7		1062	33	264	8	237	7	1533	48	126	4	

Underlying respiratory condition at discharge									-0.10																0.06
Chronic respiratory condition[7]	10485	(| 76 |)	10007	(| 95 |)	478	(| 5 |)		2632	(| 25 |)	767	(| 7 |)	756	(| 7 |)	6033	(| 58 |)	297	(| 3 |)	
None	3339	(| 24 |)	3152	(| 94 |)	187	(| 6 |)		927	(| 28 |)	254	(| 8 |)	224	(| 7 |)	1841	(| 55 |)	93	(| 3 |)	
Underlying non-respiratory condition at discharge									-0.19																0.07
Chronic non-respiratory condition[8]	13669	(| 99 |)	13030	(| 95 |)	639	(| 5 |)		3499	(| 26 |)	1006	(| 7 |)	970	(| 7 |)	7808	(| 57 |)	386	(| 3 |)	
None	155	(| 1 |)	129	(| 83 |)	26	(| 17 |)		60	(| 39 |)	15	(| 10 |)	10	(| 6 |)	66	(| 43 |)	4	(| 3 |)	
COVID-19-like illness (CLI) ICD discharge codes									0.66																0.00
≥1 CLI clinical diagnosis code[9]	10838	(| 78 |)	10187	(| 94 |)	651	(| 6 |)		2792	(| 26 |)	804	(| 7 |)	784	(| 7 |)	6159	(| 57 |)	299	(| 3 |)	
No clinical diagnosis but ≥1 CLI sign or symptom[10]	2986	(| 22 |)	2972	(| 100 |)	14	(| 0 |)		767	(| 26 |)	217	(| 7 |)	196	(| 7 |)	1715	(| 57 |)	91	(| 3 |)	
CLI diagnosis and placement among discharge codes									0.17																-0.06
CLI is first or primary diagnosis	255	(| 2 |)	224	(| 88 |)	31	(| 12 |)		89	(| 35 |)	20	(| 8 |)	18	(| 7 |)	118	(| 46 |)	10	(| 4 |)	
CLI is not first or primary diagnosis	13569	(| 98 |)	12935	(| 95 |)	634	(| 5 |)		3470	(| 26 |)	1001	(| 7 |)	962	(| 7 |)	7756	(| 57 |)	380	(| 3 |)	
Intensive care unit (ICU) admissions									-0.02																-0.05
Admitted to ICU	2380	(| 17 |)	2270	(| 95 |)	110	(| 5 |)		664	(| 28 |)	200	(| 8 |)	159	(| 7 |)	1279	(| 54 |)	78	(| 3 |)	
Not in ICU during hospitalization	11444	(| 83 |)	10889	(| 95 |)	555	(| 5 |)		2895	(| 25 |)	821	(| 7 |)	821	(| 7 |)	6595	(| 58 |)	312	(| 3 |)	
COVID-19 Vaccinations									1.16																-
Unvaccinated	3559	(| 26 |)	3071	(| 86 |)	488	(| 14 |)		3559	(| 100 |)															
BNT162b2 (Pfizer-BioNTech)	5668	(| 41 |)	5564	(| 98 |)	104	(| 2 |)						473	(| 8 |)	517	(| 9 |)	4678	(| 83 |)					
mRNA-1273 (Moderna)	4207	(| 30 |)	4144	(| 99 |)	63	(| 1 |)						548	(| 13 |)	463	(| 11 |)	3196	(| 76 |)					
Ad26.COV2.S (Johnson & Johnson)	390	(| 3 |)	380	(| 97 |)	10	(| 3 |)																390	(| 100 |)	

Abbreviations: Standard Mean Difference (SMD), COVID-like Illness (CLI), International Classification of Disease (ICD), Intensive Care Unit (ICU), Emergency Department (ED), Urgent Care (UC)

[1]Partially vaccinated with 1 dose: patients received dose-1 of mRNA vaccine ≥ 14 days prior to the index text date, had not received dose-2 by the index test date

[2]Partially vaccinated with 2 doses: patients received dose-1 and dose-2 of mRNA vaccine, dose-2 receipt date 1-13 days prior to index date.

[3]Fully vaccinated: patients received single dose of J&J vaccine, dose-1 and dose-2 of mRNA vaccine, dose-2 of mRNA vaccine ≥ 14 days prior to the index text date.

[4]Standard Mean Difference (SMD) calculation compares unvaccinated to any receipt of vaccine (partial dose-1, partial dose-2 and full vaccination).

[5]Index date for each medical encounter was defined as the date of respiratory specimen collection associated with the most recent positive or negative SARS-CoV-2 test result prior to the medical encounter or the date of the medical encounter if testing only occurred after the admission or encounter date.

[6]Other race include Asian, Hawaiian or Other Pacific islander, American Indian or Alaskan Native, Other not-listed and multi-race.

[7]Underlying chronic respiratory conditions include asthma, chronic obstructive pulmonary disease (COPD), other lung disease.

[8]Underlying chronic non-respiratory conditions include: heart failure, ischemic heart disease, hypertension, other heart disease, stroke, other cerebrovascular disease, diabetes (type 1, 2 and due to other specified conditions), other metabolic disease, clinical obesity, clinically underweight, renal disease, liver disease, blood disorder, other immunosuppressive conditions, organ transplant recipient, cancer, dementia, neurological/musculoskeletal disorder or Down's syndrome.

[9]CLI clinical discharge diagnosis codes include: COVID-19 U codes, COVID-19 pneumonia, influenza pneumonia, other viral pneumonia, pneumonia and influenza (bacterial and other) influenza diagnoses, acute respiratory distress syndrome (ARDS), COPD exacerbation, asthma exacerbation, respiratory failure, other acute lower respiratory tract infection, sinusitis, acute upper respiratory tract infection.

[10]CLI signs and symptoms include: hemoptysis, cough, dyspnea unspecified, chest pain or breathing/painful respiration, asphyxia, hypoxemia, pleurisy, respiratory arrest, abnormal sputum, other specified symptoms and signs involving the circulatory and respiratory systems, fever, chills (without fever), diarrhea, disturbance of taste or smell, headache, myalgia, sepsis, other malaise, other fatigue, shock (unspecified), debility (unspecified), altered level of consciousness/mental state, weakness, nausea and vomiting, rash or other nonspecific skin eruption, abdominal pain

Table S10. Characteristics of adults with medically attended COVID-19-like illness and the percent with laboratory-confirmed SARS-CoV-2 infection and percent unvaccinated, partially vaccinated with messenger RNA (mRNA) vaccines, or fully vaccinated with mRNA or Ad26.COV2.S vaccines, REGENSTRIEF INSTITUTE

	Total Medical Events	SARS-CoV-2 Negatives	SARS-CoV-2 Positives		Unvaccinated	Partially mRNA Vaccinated (1 dose)[1]	Partially mRNA Vaccinated (2 doses)[2]	Fully mRNA Vaccinated[3]	Fully Ad26.COV2.S Vaccinated[3]	
	N (Col. %)	N (Row %)	N (Row %)	SMD	N (Row %)	N (Row %)	N (Row %)	N (Row %)	N (Row %)	SMD[4]
A. Hospitalizations										
All hospitalizations	12437 (100)	10776 (87)	1661 (13)		7593 (61)	925 (7)	674 (5)	3114 (25)	131 (1)	
Month of hospitalization index date[5]				0.3						0.36
January	536 (4)	387 (72)	149 (28)		489 (91)	35 (7)	12 (2)	0 (0)	0 (0)	
February	1828 (15)	1594 (87)	234 (13)		1318 (72)	268 (15)	180 (10)	62 (3)	0 (0)	
March	2863 (23)	2589 (90)	274 (10)		1779 (62)	249 (9)	250 (9)	581 (20)	4 (0)	
April	3257 (26)	2762 (85)	495 (15)		1908 (59)	217 (7)	143 (4)	951 (29)	38 (1)	
May	3105 (25)	2652 (85)	453 (15)		1672 (54)	137 (4)	81 (3)	1151 (37)	64 (2)	
June	848 (7)	792 (93)	56 (7)		427 (50)	19 (2)	8 (1)	369 (44)	25 (3)	
Site-regions				0.31						0.28
Site-region 1	2797 (22)	2386 (85)	411 (15)		1966 (70)	173 (6)	114 (4)	514 (18)	30 (1)	
Site-region 2	565 (5)	458 (81)	107 (19)		317 (56)	44 (8)	16 (3)	180 (32)	8 (1)	
Site-region 3	170 (1)	122 (72)	48 (28)		116 (68)	9 (5)	8 (5)	37 (22)	0 (0)	
Site-region 4	934 (8)	779 (83)	155 (17)		577 (62)	63 (7)	63 (7)	222 (24)	9 (1)	
Site-region 5	3754 (30)	3334 (89)	420 (11)		2181 (58)	302 (8)	223 (6)	1002 (27)	46 (1)	
Site-region 6	1151 (9)	991 (86)	160 (14)		681 (59)	104 (9)	65 (6)	293 (25)	8 (1)	
Site-region 7	114 (1)	108 (95)	6 (5)		64 (56)	8 (7)	7 (6)	33 (29)	2 (2)	
Site-region 8	856 (7)	735 (86)	121 (14)		513 (60)	65 (8)	51 (6)	224 (26)	3 (0)	
Site-region 9	778 (6)	711 (91)	67 (9)		371 (48)	65 (8)	50 (6)	279 (36)	13 (2)	
Site-region 10	271 (2)	256 (94)	15 (6)		142 (52)	19 (7)	13 (5)	95 (35)	2 (1)	
Site-region missing	1047 (8)	896 (86)	151 (14)		665 (64)	73 (7)	64 (6)	235 (22)	10 (1)	
Age groups				0.25						0.39
50-64 years	3158 (25)	2583 (82)	575 (18)		2323 (74)	208 (7)	127 (4)	431 (14)	69 (2)	
65-74 years	3988 (32)	3488 (87)	500 (13)		2483 (62)	293 (7)	202 (5)	973 (24)	37 (1)	
75-84 years	3382 (27)	2997 (89)	385 (11)		1842 (54)	261 (8)	204 (6)	1057 (31)	18 (1)	
≥85 years	1909 (15)	1708 (89)	201 (11)		945 (50)	163 (9)	141 (7)	653 (34)	7 (0)	
Race (regardless of ethnicity)				0.11						0.22
White	8916 (72)	7797 (87)	1119 (13)		5360 (60)	693 (8)	513 (6)	2268 (25)	82 (1)	

Black	1385 (11)	1174 (85)	211 (15)		1025 (74)	77 (6)	55 (4)	206 (15)	22 (2)	
Other[6]	84 (1)	65 (77)	19 (23)		49 (58)	3 (4)	9 (11)	23 (27)	0 (0)	
Unknown	2052 (16)	1740 (85)	312 (15)		1159 (56)	152 (7)	97 (5)	617 (30)	27 (1)	
Ethnicity (regardless of race)				0.13						0.15
Hispanic	207 (2)	166 (80)	41 (20)		159 (77)	9 (4)	3 (1)	34 (16)	2 (1)	
Non-Hispanic	10263 (83)	8960 (87)	1303 (13)		6365 (62)	763 (7)	577 (6)	2455 (24)	103 (1)	
Unknown	1967 (16)	1650 (84)	317 (16)		1069 (54)	153 (8)	94 (5)	625 (32)	26 (1)	
Underlying respiratory condition at discharge				-0.09						0.00
Chronic respiratory condition[7]	6790 (55)	5951 (88)	839 (12)		4141 (61)	517 (8)	360 (5)	1707 (25)	65 (1)	
None	5647 (45)	4825 (85)	822 (15)		3452 (61)	408 (7)	314 (6)	1407 (25)	66 (1)	
Underlying non-respiratory condition at discharge				-0.25						0.07
Chronic non-respiratory condition[8]	9282 (75)	8208 (88)	1074 (12)		5571 (60)	714 (8)	519 (6)	2369 (26)	109 (1)	
None	3155 (25)	2568 (81)	587 (19)		2022 (64)	211 (7)	155 (5)	745 (24)	22 (1)	
COVID-19-like illness (CLI) ICD discharge codes				0.88						-0.12
≥1 CLI clinical diagnosis code[9]	8550 (69)	6950 (81)	1600 (19)		5383 (63)	620 (7)	432 (5)	2027 (24)	88 (1)	
No clinical diagnosis but ≥1 CLI sign or symptom[10]	3887 (31)	3826 (98)	61 (2)		2210 (57)	305 (8)	242 (6)	1087 (28)	43 (1)	
CLI diagnosis and placement among discharge codes				0.65						-0.11
CLI is first or primary diagnosis	5495 (44)	4321 (79)	1174 (21)		3511 (64)	393 (7)	283 (5)	1250 (23)	58 (1)	
CLI is not first or primary diagnosis	6942 (56)	6455 (93)	487 (7)		4082 (59)	532 (8)	391 (6)	1864 (27)	73 (1)	
Intensive care unit (ICU) admissions				0.05						-0.08
Admitted to ICU	2236 (18)	1911 (85)	325 (15)		1457 (65)	149 (7)	104 (5)	509 (23)	17 (1)	
Not in ICU during hospitalization	10201 (82)	8865 (87)	1336 (13)		6136 (60)	776 (8)	570 (6)	2605 (26)	114 (1)	
COVID-19 Vaccinations				0.71						
Unvaccinated	7593 (61)	6156 (81)	1437 (19)		7593 (100)	0 (0)	0 (0)	0 (0)	0 (0)	
BNT162b2 (Pfizer-BioNTech)	2050 (16)	1949 (95)	101 (5)		0 (0)	352 (17)	320 (16)	1378 (67)	0 (0)	
mRNA-1273 (Moderna)	2663 (21)	2553 (96)	110 (4)		0 (0)	573 (22)	354 (13)	1736 (65)	0 (0)	
Ad26.COV2.S (Johnson & Johnson)	131 (1)	118 (90)	13 (10)		0 (0)	0 (0)	0 (0)	0 (0)	131 (100)	

B. Emergency Department (ED) and Urgent Care (UC) Visits

All ED and UC Visits	7847 (100)	6394 (81)	1453 (19)		5100 (65)	572 (7)	385 (5)	1663 (21)	127 (2)	
By medical event setting										
ED visits	7847 (100)	6394 (81)	1453 (19)		5100 (65)	572 (7)	385 (5)	1663 (21)	127 (2)	
Month of ED/UC event index date[5]				0.25						0.31
January	281 (4)	192 (68)	89 (32)		265 (94)	14 (5)	1 (0)	1 (0)	0 (0)	
February	884 (11)	749 (85)	135 (15)		634 (72)	137 (15)	82 (9)	31 (4)	0 (0)	
March	1682 (21)	1411 (84)	271 (16)		1164 (69)	145 (9)	126 (7)	243 (14)	4 (0)	
April	2159 (28)	1676 (78)	483 (22)		1361 (63)	160 (7)	103 (5)	494 (23)	41 (2)	
May	2082 (27)	1705 (82)	377 (18)		1257 (60)	92 (4)	62 (3)	613 (29)	58 (3)	
June	759 (10)	661 (87)	98 (13)		419 (55)	24 (3)	11 (1)	281 (37)	24 (3)	
Site-regions				0.38						0.18
Site-region 1	894 (11)	705 (79)	189 (21)		658 (74)	58 (6)	40 (4)	129 (14)	9 (1)	
Site-region 2	518 (7)	420 (81)	98 (19)		316 (61)	23 (4)	17 (3)	148 (29)	14 (3)	
Site-region 3	291 (4)	156 (54)	135 (46)		216 (74)	27 (9)	16 (5)	30 (10)	2 (1)	
Site-region 4	884 (11)	695 (79)	189 (21)		574 (65)	65 (7)	47 (5)	184 (21)	14 (2)	
Site-region 5	2339 (30)	1968 (84)	371 (16)		1455 (62)	180 (8)	136 (6)	528 (23)	40 (2)	
Site-region 6	639 (8)	530 (83)	109 (17)		445 (70)	49 (8)	30 (5)	107 (17)	8 (1)	
Site-region 7	176 (2)	153 (87)	23 (13)		119 (68)	12 (7)	7 (4)	35 (20)	3 (2)	
Site-region 8	711 (9)	581 (82)	130 (18)		477 (67)	45 (6)	27 (4)	151 (21)	11 (2)	
Site-region 9	398 (5)	344 (86)	54 (14)		233 (59)	37 (9)	20 (5)	101 (25)	7 (2)	
Site-region 10	191 (2)	179 (94)	12 (6)		112 (59)	14 (7)	13 (7)	52 (27)	0 (0)	
Site-region missing	806 (10)	663 (82)	143 (18)		495 (61)	62 (8)	32 (4)	198 (25)	19 (2)	
Age groups				0.33						0.41
50-64 years	3323 (42)	2556 (77)	767 (23)		2502 (75)	211 (6)	112 (3)	406 (12)	92 (3)	
65-74 years	2264 (29)	1862 (82)	402 (18)		1384 (61)	179 (8)	131 (6)	548 (24)	22 (1)	
75-84 years	1591 (20)	1368 (86)	223 (14)		871 (55)	133 (8)	99 (6)	479 (30)	9 (1)	
≥85 years	669 (9)	608 (91)	61 (9)		343 (51)	49 (7)	43 (6)	230 (34)	4 (1)	
Race (regardless of ethnicity)				0.11						0.16
White	5346 (68)	4417 (83)	929 (17)		3447 (64)	403 (8)	271 (5)	1144 (21)	81 (2)	
Black	612 (8)	474 (77)	138 (23)		470 (77)	36 (6)	21 (3)	76 (12)	9 (1)	
Other[6]	56 (1)	37 (66)	19 (34)		38 (68)	3 (5)	5 (9)	10 (18)	0 (0)	
Unknown	1833 (23)	1466 (80)	367 (20)		1145 (62)	130 (7)	88 (5)	433 (24)	37 (2)	
Ethnicity (regardless of race)				0.14						0.11

Hispanic	133 (2)	92 (69)	41 (31)		108 (81)	5 (4)	1 (1)	14 (11)	5 (4)	
Non-Hispanic	5884 (75)	4825 (82)	1059 (18)		3855 (66)	446 (8)	300 (5)	1198 (20)	85 (1)	
Unknown	1830 (23)	1477 (81)	353 (19)		1137 (62)	121 (7)	84 (5)	451 (25)	37 (2)	
Underlying respiratory condition at discharge				-0.44						0.05
Chronic respiratory condition[7]	1824 (23)	1680 (92)	144 (8)		1146 (63)	133 (7)	95 (5)	414 (23)	36 (2)	
None	6023 (77)	4714 (78)	1309 (22)		3954 (66)	439 (7)	290 (5)	1249 (21)	91 (2)	
Underlying non-respiratory condition at discharge				-0.30						0.12
Chronic non-respiratory condition[8]	2723 (35)	2379 (87)	344 (13)		1668 (61)	196 (7)	138 (5)	685 (25)	36 (1)	
None	5124 (65)	4015 (78)	1109 (22)		3432 (67)	376 (7)	247 (5)	978 (19)	91 (2)	
COVID-19-like illness (CLI) ICD discharge codes				1.07						-0.21
≥1 CLI clinical diagnosis code[9]	4031 (51)	2752 (68)	1279 (32)		2802 (70)	267 (7)	155 (4)	739 (18)	68 (2)	
No clinical diagnosis but ≥1 CLI sign or symptom[10]	3816 (49)	3642 (95)	174 (5)		2298 (60)	305 (8)	230 (6)	924 (24)	59 (2)	
CLI diagnosis and placement among discharge codes				0.59						-0.16
CLI is first or primary diagnosis	5330 (68)	4055 (76)	1275 (24)		3598 (68)	376 (7)	253 (5)	1010 (19)	93 (2)	
CLI is not first or primary diagnosis	2517 (32)	2339 (93)	178 (7)		1502 (60)	196 (8)	132 (5)	653 (26)	34 (1)	
COVID-19 Vaccinations				0.73						
Unvaccinated	5100 (65)	3800 (75)	1300 (25)		5100 (100)	0 (0)	0 (0)	0 (0)	0 (0)	
BNT162b2 (Pfizer-BioNTech)	1175 (15)	1106 (94)	69 (6)		0 (0)	224 (19)	167 (14)	784 (67)	0 (0)	
mRNA-1273 (Moderna)	1445 (18)	1373 (95)	72 (5)		0 (0)	348 (24)	218 (15)	879 (61)	0 (0)	
Ad26.COV2.S (Johnson & Johnson)	127 (2)	115 (91)	12 (9)		0 (0)	0 (0)	0 (0)	0 (0)	127 (100)	

Note: All patients with indeterminate immunization status (receipt of dose-1 of mRNA vaccine 1-13 days prior to index test date) were excluded from table.

Abbreviations: Standard Mean Difference (SMD), COVID-like Illness (CLI), International Classification of Disease (ICD), Intensive Care Unit (ICU), Emergency Department (ED), Urgent Care (UC)

[1]Partially vaccinated with 1 dose: patients received dose-1 of mRNA vaccine ≥ 14 days prior to the index text date, had not received dose-2 by the index test date.

[2]Partially vaccinated with 2 doses: patients received dose-1 and dose-2 of mRNA vaccine, dose-2 receipt date 1-13 days prior to index date.

[3]Fully vaccinated: patients received single dose of J&J vaccine, dose-1 and dose-2 of mRNA vaccine, dose-2 of mRNA vaccine ≥ 14 days prior to the index text date.

[4]Standard Mean Difference (SMD) calculation compares unvaccinated to any receipt of vaccine (partial dose-1, partial dose-2 and full vaccination).

[5]Index date for each medical encounter was defined as the date of respiratory specimen collection associated with the most recent positive or negative SARS-CoV-2 test result prior to the medical encounter or the date of the medical encounter if testing only occurred after the admission or encounter date.

[6]Other race include Asian, Hawaiian or Other Pacific islander, American Indian or Alaskan Native, Other not-listed and multi-race.

[7]Underlying chronic respiratory conditions include asthma, chronic obstructive pulmonary disease (COPD), other lung disease.

[8]Underlying chronic non-respiratory conditions include: heart failure, ischemic heart disease, hypertension, other heart disease, stroke, other cerebrovascular disease, diabetes (type 1, 2 and due to other specified conditions), other metabolic disease, clinical obesity, clinically underweight, renal disease, liver disease, blood disorder, other immunosuppressive conditions, organ transplant recipient, cancer, dementia, neurological/musculoskeletal disorder or Down's syndrome.

[9]CLI clinical discharge diagnosis codes include: COVID-19 U codes, COVID-19 pneumonia, influenza pneumonia, other viral pneumonia, pneumonia and influenza (bacterial and other) influenza diagnoses, acute respiratory distress syndrome (ARDS), COPD exacerbation, asthma exacerbation, respiratory failure, other acute lower respiratory tract infection, sinusitis, acute upper respiratory tract infection.

[10]CLI signs and symptoms include: hemoptysis, cough, dyspnea unspecified, chest pain or breathing/painful respiration, asphyxia, hypoxemia, pleurisy, respiratory arrest, abnormal sputum, other specified symptoms and signs involving the circulatory and respiratory systems, fever, chills (without fever), diarrhea, disturbance of taste or smell, headache, myalgia, sepsis, other malaise, other fatigue, shock (unspecified), debility (unspecified), altered level of consciousness/mental state, weakness, nausea and vomiting, rash or other nonspecific skin eruption, abdominal pain

Table S11. Characteristics of adults with medically attended COVID-19-like illness and the percent with laboratory-confirmed SARS-CoV-2 infection and percent unvaccinated, partially vaccinated with messenger RNA (mRNA) vaccines, or fully vaccinated with mRNA or Ad26.COV2.S vaccines, UNIVERSITY OF COLORADO

	Total Medical Events	SARS-CoV-2 Negatives	SARS-CoV-2 Positives		Unvaccinated	Partially mRNA Vaccinated (1 dose)[1]	Partially mRNA Vaccinated (2 doses)[2]	Fully mRNA Vaccinated[3]	Fully Ad26.COV2.S Vaccinated[3]	
	N (Col. %)	N (Row %)	N (Row %)	SMD	N (Row %)	N (Row %)	N (Row %)	N (Row %)	N (Row %)	SMD[4]
A. Hospitalizations										
All hospitalizations	5314 (100)	4723 (89)	591 (11)		3861 (73)	221 (4)	211 (4)	1021 (19)	0 (0)	
Month of hospitalization index date[5]				0.31						0.27
January	270 (5)	225 (83)	45 (17)		247 (91)	17 (6)	6 (2)	0 (0)	0 (0)	
February	777 (15)	700 (90)	77 (10)		614 (79)	73 (9)	52 (7)	38 (5)	0 (0)	
March	1125 (21)	1038 (92)	87 (8)		772 (69)	59 (5)	82 (7)	212 (19)	0 (0)	
April	1605 (30)	1407 (88)	198 (12)		1160 (72)	41 (3)	56 (3)	348 (22)	0 (0)	
May	1408 (26)	1231 (87)	177 (13)		988 (70)	24 (2)	14 (1)	382 (27)	0 (0)	
June	129 (2)	122 (95)	7 (5)		80 (62)	7 (5)	1 (1)	41 (32)	0 (0)	
Site-regions				0.04						0.37
Site-region 1	1585 (30)	1413 (89)	172 (11)		1153 (73)	64 (4)	62 (4)	306 (19)	0 (0)	
Site-region 2	1927 (36)	1719 (89)	208 (11)		1239 (64)	106 (6)	98 (5)	484 (25)	0 (0)	
Site-region 3	1802 (34)	1591 (88)	211 (12)		1469 (82)	51 (3)	51 (3)	231 (13)	0 (0)	
Age groups				0.32						0.40
50-64 years	1195 (22)	989 (83)	206 (17)		1020 (85)	36 (3)	41 (3)	98 (8)	0 (0)	
65-74 years	1787 (34)	1615 (90)	172 (10)		1302 (73)	68 (4)	73 (4)	344 (19)	0 (0)	
75-84 years	1518 (29)	1375 (91)	143 (9)		979 (64)	81 (5)	69 (5)	389 (26)	0 (0)	
≥85 years	814 (15)	744 (91)	70 (9)		560 (69)	36 (4)	28 (3)	190 (23)	0 (0)	
Race (regardless of ethnicity)				0.30						0.30
White	4395 (83)	3970 (90)	425 (10)		3093 (70)	189 (4)	186 (4)	927 (21)	0 (0)	
Black	338 (6)	286 (85)	52 (15)		294 (87)	11 (3)	5 (1)	28 (8)	0 (0)	
Other[6]	205 (4)	162 (79)	43 (21)		160 (78)	12 (6)	8 (4)	25 (12)	0 (0)	
Unknown	376 (7)	305 (81)	71 (19)		314 (84)	9 (2)	12 (3)	41 (11)	0 (0)	
Ethnicity (regardless of race)				0.28						0.20
Hispanic	515 (10)	414 (80)	101 (20)		418 (81)	21 (4)	21 (4)	55 (11)	0 (0)	
Non-Hispanic	4761 (90)	4279 (90)	482 (10)		3413 (72)	198 (4)	189 (4)	961 (20)	0 (0)	
Unknown	38 (1)	30 (79)	8 (21)		30 (79)	2 (5)	1 (3)	5 (13)	0 (0)	

Underlying respiratory condition at discharge				0.29				-0.08
Chronic respiratory condition[7]	3547 (67)	3084 (87)	463 (13)		2618 (74)	149 (4)	136 (4)	644 (18)	0 (0)	
None	1767 (33)	1639 (93)	128 (7)		1243 (70)	72 (4)	75 (4)	377 (21)	0 (0)	
Underlying non-respiratory condition at discharge				-0.23						0.11
Chronic non-respiratory condition[8]	5248 (99)	4684 (89)	564 (11)		3802 (72)	221 (4)	209 (4)	1016 (19)	0 (0)	
None	66 (1)	39 (59)	27 (41)		59 (89)	0 (0)	2 (3)	5 (8)	0 (0)	
COVID-19-like illness (CLI) ICD discharge codes				1.09						-0.15
≥1 CLI clinical diagnosis code[9]	3501 (66)	2913 (83)	588 (17)		2617 (75)	143 (4)	131 (4)	610 (17)	0 (0)	
No clinical diagnosis but ≥1 CLI sign or symptom[10]	1813 (34)	1810 (100)	3 (0)		1244 (69)	78 (4)	80 (4)	411 (23)	0 (0)	
CLI diagnosis and placement among discharge codes				1.73						-0.29
CLI is first or primary diagnosis	911 (17)	470 (52)	441 (48)		768 (84)	22 (2)	29 (3)	92 (10)	0 (0)	
CLI is not first or primary diagnosis	4403 (83)	4253 (97)	150 (3)		3093 (70)	199 (5)	182 (4)	929 (21)	0 (0)	
Intensive care unit (ICU) admissions				0.00						-0.06
Admitted to ICU	1454 (27)	1293 (89)	161 (11)		1086 (75)	55 (4)	49 (3)	264 (18)	0 (0)	
Not in ICU during hospitalization	3860 (73)	3430 (89)	430 (11)		2775 (72)	166 (4)	162 (4)	757 (20)	0 (0)	
COVID-19 Vaccinations				0.71						
Unvaccinated	3861 (73)	3302 (86)	559 (14)		3861 (100)	0 (0)	0 (0)	0 (0)	0 (0)	
BNT162b2 (Pfizer-BioNTech)	820 (15)	794 (97)	26 (3)		0 (0)	100 (12)	125 (15)	595 (73)	0 (0)	
mRNA-1273 (Moderna)	633 (12)	627 (99)	6 (1)		0 (0)	121 (19)	86 (14)	426 (67)	0 (0)	
Ad26.COV2.S (Johnson & Johnson)	0 (0)	0 (0)	0 (0)		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	

Note: All patients with indeterminate immunization status (receipt of dose-1 of mRNA vaccine 1-13 days prior to index test date) were excluded from table.

Abbreviations: Standard Mean Difference (SMD), COVID-like Illness (CLI), International Classification of Disease (ICD), Intensive Care Unit (ICU), Emergency Department (ED), Urgent Care (UC)

[1]Partially vaccinated with 1 dose: patients received dose-1 of mRNA vaccine ≥ 14 days prior to the index text date, had not received dose-2 by the index test date.

[2]Partially vaccinated with 2 doses: patients received dose-1 and dose-2 of mRNA vaccine, dose-2 receipt date 1-13 days prior to index date.

[3]Fully vaccinated: patients received single dose of J&J vaccine, dose-1 and dose-2 of mRNA vaccine, dose-2 of mRNA vaccine ≥ 14 days prior to the index text date.

[4]Standard Mean Difference (SMD) calculation compares unvaccinated to any receipt of vaccine (partial dose-1, partial dose-2 and full vaccination).

[5]Index date for each medical encounter was defined as the date of respiratory specimen collection associated with the most recent positive or negative SARS-CoV-2 test result prior to the medical encounter or the date of the medical encounter if testing only occurred after the admission or encounter date.

[6]Other race include Asian, Hawaiian or Other Pacific islander, American Indian or Alaskan Native, Other not-listed and multi-race.

[7]Underlying chronic respiratory conditions include asthma, chronic obstructive pulmonary disease (COPD), other lung disease.

[8]Underlying chronic non-respiratory conditions include heart failure, ischemic heart disease, hypertension, other heart disease, stroke, other cerebrovascular disease, diabetes (type 1, 2 and due to other specified conditions), other metabolic disease, clinical obesity, clinically underweight, renal disease, liver disease, blood disorder, other immunosuppressive conditions, organ transplant recipient, cancer, dementia, neurological/musculoskeletal disorder or Down's syndrome.

[9]CLI clinical discharge diagnosis codes include: COVID-19 U codes, COVID-19 pneumonia, influenza pneumonia, other viral pneumonia, pneumonia and influenza (bacterial and other) influenza diagnoses, acute respiratory distress syndrome (ARDS), COPD exacerbation, asthma exacerbation, respiratory failure, other acute lower respiratory tract infection, sinusitis, acute upper respiratory tract infection.

[10]CLI signs and symptoms include: hemoptysis, cough, dyspnea unspecified, chest pain or breathing/painful respiration, asphyxia, hypoxemia, pleurisy, respiratory arrest, abnormal sputum, other specified symptoms and signs involving the circulatory and respiratory systems, fever, chills (without fever), diarrhea, disturbance of taste or smell, headache, myalgia, sepsis, other malaise, other fatigue, shock (unspecified), debility (unspecified), altered level of consciousness/mental state, weakness, nausea and vomiting, rash or other nonspecific skin eruption, abdominal pain

Table S12. Characteristics of Full Sample - Hospitalizations

	Total Medical Events	**SARS-CoV-2 Negatives**	**SARS-CoV-2 Positives**		**Unvaccinated**	**Partially mRNA Vaccinated (1 dose)[1]**	**Partially mRNA Vaccinated (2 doses)[2]**	**Fully mRNA Vaccinated[3]**	**Fully Ad26.COV2.S Vaccinated[3]**	
	N (Col. %)	N (Row %)	N (Row %)	SMD	N (Row %)	N (Row %)	N (Row %)	N (Row %)	N (Row %)	SMD[4]
A. Hospitalizations										
All hospitalizations	41552 (100)	37231 (90)	4321 (10)		20406 (49)	3083 (7)	2482 (6)	14874 (36)	707 (2)	
Events per person				-0.13						0.05
First hospitalization per person	40367 (97)	36096 (89)	4271 (11)		19903 (49)	3003 (7)	2456 (6)	14361 (36)	644 (2)	
Repeat hospitalization per person	1185 (3)	1135 (96)	50 (4)		503 (42)	80 (7)	26 (2)	513 (43)	63 (5)	
Month of hospitalization index date[5]				0.36						0.51
January	1063 (3)	766 (72)	297 (28)		980 (92)	62 (6)	20 (2)	1 (0)	0 (0)	
February	4016 (10)	3350 (83)	666 (17)		2969 (74)	545 (14)	355 (9)	147 (4)	0 (0)	
March	8873 (21)	8084 (91)	789 (9)		4714 (53)	989 (11)	1022 (12)	2125 (24)	23 (0)	
April	12143 (29)	10873 (90)	1270 (10)		5619 (46)	801 (7)	757 (6)	4735 (39)	231 (2)	
May	11943 (29)	10843 (91)	1100 (9)		4971 (42)	560 (5)	296 (2)	5798 (49)	318 (3)	
June	3514 (8)	3315 (94)	199 (6)		1153 (33)	126 (4)	32 (1)	2068 (59)	135 (4)	
Sites				0.56						0.78
Columbia University	3126 (8)	2458 (79)	668 (21)		2181 (70)	216 (7)	103 (3)	588(19)	38 (1)	
HealthPartners	989 (2)	928 (94)	61 (6)		389 (39)	98 (10)	104 (11)	390(39)	8 (1)	
Intermountain Healthcare	3910 (9)	3353 (86)	557 (14)		1917 (49)	392 (10)	278 (7)	1236(32)	87 (2)	
Kaiser Permanente Northern California	13824 (33)	13159 (95)	665 (5)		3559 (26)	1021 (7)	980 (7)	7874(57)	390 (3)	
Kaiser Permanente Northwest	1952 (5)	1834 (94)	118 (6)		906 (46)	210 (11)	132 (7)	651(33)	53 (3)	
Regenstrief Institute	12437 (30)	10776 (87)	1661 (13)		7593 (61)	925 (7)	674 (5)	3114(25)	131 (1)	
University of Colorado	5314 (13)	4723 (89)	591 (11)		3861 (73)	221 (4)	211 (4)	1021(19)	0 (0)	
Site-regions				0.63						0.82
Columbia University - site-region 1	3126 (8)	2458 (79)	668 (21)		2181 (70)	216 (7)	103 (3)	588 (19)	38 (1)	
HealthPartners - site-region 1	973 (2)	916 (94)	57 (6)		381 (39)	93 (10)	103 (11)	388 (40)	8 (1)	
HealthPartners - site-region 2	16 (0)	12 (75)	<5		8 (50)	5 (31)	<5	<5	0 (0)	
Intermountain Healthcare - site-region 1	248 (1)	219 (88)	29 (12)		133 (54)	19 (8)	16 (6)	71 (29)	9 (4)	

Intermountain Healthcare - site-region 2	238 (1)	204 (86)	34 (14)	101 (42)	27 (11)	13 (5)	93 (39)	4 (2)
Intermountain Healthcare - site-region 3	1434 (3)	1253 (87)	181 (13)	654 (46)	147 (10)	95 (7)	510 (36)	28 (2)
Intermountain Healthcare - site-region 4	721 (2)	630 (87)	91 (13)	340 (47)	66 (9)	52 (7)	257 (36)	6 (1)
Intermountain Healthcare - site-region 5	67 (0)	58 (87)	9 (13)	34 (51)	6 (9)	9 (13)	17 (25)	1 (1)
Intermountain Healthcare - site-region 6	479 (1)	411 (86)	68 (14)	245 (51)	51 (11)	38 (8)	133 (28)	12 (3)
Intermountain Healthcare - site-region 7	74 (0)	61 (82)	13 (18)	37 (50)	7 (9)	9 (12)	20 (27)	1 (1)
Intermountain Healthcare - site-region 8	649 (2)	517 (80)	132 (20)	373 (57)	69 (11)	46 (7)	135 (21)	26 (4)
Kaiser Permanente Northern California – site-region 1	705 (2)	651 (92)	54 (8)	223 (32)	68 (10)	49 (7)	347 (49)	18 (3)
Kaiser Permanente Northern California – site-region 2	510 (1)	453 (89)	57 (11)	211 (41)	41 (8)	25 (5)	225 (44)	8 (2)
Kaiser Permanente Northern California – site-region 3	3200 (8)	2981 (93)	219 (7)	997 (31)	255 (8)	204 (6)	1683 (53)	61 (2)
Kaiser Permanente Northern California – site-region 4	5660 (14)	5478 (97)	182 (3)	1262 (22)	370 (7)	432 (8)	3410 (60)	186 (3)
Kaiser Permanente Northern California – site-region 5	1660 (4)	1605 (97)	55 (3)	338 (20)	117 (7)	118 (7)	1023 (62)	64 (4)
Kaiser Permanente Northern California – site-region 6	676 (2)	663 (98)	13 (2)	123 (18)	57 (8)	47 (7)	428 (63)	21 (3)
Kaiser Permanente Northern California – site-region 7	267 (1)	243 (91)	24 (9)	91 (34)	19 (7)	20 (7)	132 (49)	5 (2)
Kaiser Permanente Northern California – site-region 8	1146 (3)	1085 (95)	61 (5)	314 (27)	94 (8)	85 (7)	626 (55)	27 (2)
Kaiser Permanente Northwest - site-region 1	1376 (3)	1301 (95)	75 (5)	624 (45)	159 (12)	92 (7)	455 (33)	46 (3)
Kaiser Permanente Northwest - site-region 2	394 (1)	362 (92)	32 (8)	204 (52)	36 (9)	20 (5)	128 (32)	6 (2)
Kaiser Permanente Northwest - site-region 3	182 (0)	171 (94)	11 (6)	78 (43)	15 (8)	20 (11)	68 (37)	1 (1)
Regenstrief Institute - site-region 1	2797 (7)	2386 (85)	411 (15)	1966 (70)	173 (6)	114 (4)	514 (18)	30 (1)
Regenstrief Institute - site-region 2	565 (1)	458 (81)	107 (19)	317 (56)	44 (8)	16 (3)	180 (32)	8 (1)
Regenstrief Institute - site-region 3	170 (0)	122 (72)	48 (28)	116 (68)	9 (5)	8 (5)	37 (22)	0 (0)
Regenstrief Institute - site-region 4	934 (2)	779 (83)	155 (17)	577 (62)	63 (7)	63 (7)	222 (24)	9 (1)
Regenstrief Institute - site-region 5	3754 (9)	3334 (89)	420 (11)	2181 (58)	302 (8)	223 (6)	1002 (27)	46 (1)
Regenstrief Institute - site-region 6	1151 (3)	991 (86)	160 (14)	681 (59)	104 (9)	65 (6)	293 (25)	8 (1)
Regenstrief Institute - site-region 7	114 (0)	108 (95)	6 (5)	64 (56)	8 (7)	7 (6)	33 (29)	2 (2)
Regenstrief Institute - site-region 8	856 (2)	735 (86)	121 (14)	513 (60)	65 (8)	51 (6)	224 (26)	3 (0)
Regenstrief Institute - site-region 9	778 (2)	711 (91)	67 (9)	371 (48)	65 (8)	50 (6)	279 (36)	13 (2)
Regenstrief Institute - site-region 10	271 (1)	256 (94)	15 (6)	142 (52)	19 (7)	13 (5)	95 (35)	2 (1)
Regenstrief Institute - site-region missing	1047 (3)	896 (86)	151 (14)	665 (64)	73 (7)	64 (6)	235 (22)	10 (1)
University of Colorado - site-region 1	1585 (4)	1413 (89)	172 (11)	1153 (73)	64 (4)	62 (4)	306 (19)	0 (0)

University of Colorado - site-region 2	1927 (5)	1719 (89)	208 (11)		1239 (64)	106 (6)	98 (5)	484 (25)	0 (0)	
University of Colorado - site-region 3	1802 (4)	1591 (88)	211 (12)		1469 (82)	51 (3)	51 (3)	231 (13)	0 (0)	
Age groups				0.26						0.34
50-64 years	8764 (21)	7436 (85)	1328 (15)		5532 (63)	585 (7)	467 (5)	1898(22)	282 (3)	
65-74 years	13158 (32)	11839 (90)	1319 (10)		6681 (51)	1014 (8)	795 (6)	4481(34)	187 (1)	
75-84 years	12282 (30)	11193 (91)	1089 (9)		5233 (43)	935 (8)	772 (6)	5189(42)	153 (1)	
≥85 years	7348 (18)	6763 (92)	585 (8)		2960 (40)	549 (7)	448 (6)	3306(45)	85 (1)	
Race (regardless of ethnicity)				0.29						0.27
White	29019 (70)	26357 (91)	2662 (9)		13886 (48)	2246 (8)	1779 (6)	10655(37)	453 (2)	
Black	3902 (9)	3414 (87)	488 (13)		2393 (61)	269 (7)	194 (5)	961(25)	85 (2)	
Other[6]	2892 (7)	2692 (93)	200 (7)		913 (32)	183 (6)	223 (8)	1496(52)	77 (3)	
Unknown	5739 (14)	4768 (83)	971 (17)		3214 (56)	385 (7)	286 (5)	1762(31)	92 (2)	
Ethnicity (regardless of race)				0.23						0.07
Hispanic	4574 (11)	3825 (84)	749 (16)		2376 (52)	307 (7)	264 (6)	1540(34)	87 (2)	
Non-Hispanic	31069 (75)	28190 (91)	2879 (9)		15361 (49)	2318 (7)	1863 (6)	11067(36)	460 (1)	
Unknown	5909 (14)	5216 (88)	693 (12)		2669 (45)	458 (8)	355 (6)	2267(38)	160 (3)	
Underlying respiratory condition at discharge				-0.06						
Chronic respiratory condition[7]	27423 (66)	24689 (90)	2734 (10)		13018 (47)	2033 (7)	1634 (6)	10257(37)	481 (2)	
None	14129 (34)	12542 (89)	1587 (11)		7388 (52)	1050 (7)	848 (6)	4617(33)	226 (2)	
Underlying non-respiratory condition at discharge				-0.26						0.18
Chronic non-respiratory condition[8]	37899 (91)	34289 (90)	3610 (10)		18089 (48)	2835 (7)	2302 (6)	13999(37)	674 (2)	
None	3653 (9)	2942 (81)	711 (19)		2317 (63)	248 (7)	180 (5)	875(24)	33 (1)	
COVID-19-like illness (CLI) ICD discharge codes				0.85						-0.02
≥1 CLI clinical diagnosis code[9]	29941 (72)	25706 (86)	4235 (14)		14805 (49)	2191 (7)	1748 (6)	10686(36)	511 (2)	
No clinical diagnosis but ≥1 CLI sign or symptom[10]	11611 (28)	11525 (99)	86 (1)		5601 (48)	892 (8)	734 (6)	4188(36)	196 (2)	
CLI diagnosis and placement among discharge codes				1.07						-0.37
CLI is first or primary diagnosis	8699 (21)	6005 (69)	2694 (31)		5815 (67)	600 (7)	400 (5)	1770(20)	114 (2)	
CLI is not first or primary diagnosis	32853 (79)	31226 (95)	1627 (5)		14591 (44)	2483 (8)	2082 (6)	13104(40)	593 (2)	

Intensive care unit (ICU) admissions				0.01					-0.10
Admitted to ICU	7394 (18)	6606 (89)	788 (11)		4024 (54)	512 (7)	388 (5)	2359(32)	111 (2)	
Not in ICU during hospitalization	34158 (82)	30625 (90)	3533 (10)		16382 (48)	2571 (8)	2094 (6)	12515(37)	596 (2)	
COVID-19 Vaccinations				0.95						NA
Unvaccinated	20406 (49)	16711 (82)	3695 (18)		20406 (100)					
BNT162b2 (Pfizer-BioNTech)	11292 (27)	10932 (97)	360 (3)			1444 (13)	1348 (12)	8500(75)		
mRNA-1273 (Moderna)	9147 (22)	8911 (97)	236 (3)			1639 (18)	1134 (12)	6374(70)		
Ad26.COV2.S (Johnson & Johnson)	707 (2)	677 (96)	30 (4)						707 (100)	

Note: All patients with indeterminate immunization status (receipt of dose-1 of mRNA vaccine 1-13 days prior to index test date) were excluded.

Abbreviations: Standardized Mean Difference (SMD), COVID-like Illness (CLI), International Classification of Disease (ICD), Intensive Care Unit (ICU), Emergency Department (ED), Urgent Care (UC), Not Applicable (NA)

[1]Partially vaccinated with 1 dose: patients received dose-1 of mRNA vaccine ≥ 14 days prior to the index text date had not received dose-2 by the index test date.

[2]Partially vaccinated with 2 doses: patients received dose-1 and dose-2 of mRNA vaccine, dose-2 receipt date 1-13 days prior to index date.

[3]Fully vaccinated: patients received single dose of J&J vaccine, dose-1 and dose-2 of mRNA vaccine, or dose-2 of mRNA vaccine ≥ 14 days prior to the index text date.

[4]Standardized Mean Difference (SMD) calculation compares unvaccinated to any receipt of vaccine (partial dose-1, partial dose-2 and full vaccination).

5Index date for each medical encounter was defined as the date of respiratory specimen collection associated with the most recent positive or negative SARS-CoV-2 test result prior to the medical encounter or the date of the medical encounter if testing only occurred after the admission or encounter date.

[6]Other race include Asian, Hawaiian or Other Pacific islander, American Indian or Alaskan Native, Other not-listed and multi-race.

[7]Underlying chronic respiratory conditions include asthma, chronic obstructive pulmonary disease (COPD), other lung disease.

[8]Underlying chronic non-respiratory conditions include: heart failure, ischemic heart disease, hypertension, other heart disease, stroke, other cerebrovascular disease, diabetes (type 1, 2 and due to other specified conditions), other metabolic disease, clinical obesity, clinically underweight, renal disease, liver disease, blood disorder, other immunosuppressive conditions, organ transplant recipient, cancer, dementia, neurological/musculoskeletal disorder or Down's syndrome.

[9]CLI clinical discharge diagnosis codes include: COVID-19 U codes, COVID-19 pneumonia, influenza pneumonia, other viral pneumonia, pneumonia and influenza (bacterial and other), influenza disease, acute respiratory distress syndrome (ARDS), COPD exacerbation, asthma exacerbation, respiratory failure, other acute lower respiratory tract infection, sinusitis, acute upper respiratory tract infection.

[10]CLI signs and symptoms include: hemoptysis, cough, dyspnea unspecified, chest pain or breathing/painful respiration, asphyxia, hypoxemia, pleurisy, respiratory arrest, abnormal sputum, other specified symptoms and signs involving the circulatory and respiratory systems, fever, chills (without fever), diarrhea, disturbance of taste or smell, headache, myalgia, sepsis, other malaise, other fatigue, shock (unspecified), debility (unspecified), altered level of consciousness/mental state, weakness, nausea and vomiting, rash or other nonspecific skin eruption, abdominal pain

Table S13. Characteristics of Full Sample – ED/UC

	Total Medical Events	SARS-CoV-2 Negatives	SARS-CoV-2 Positives		Unvaccinated	Partially mRNA Vaccinated (1 dose)[1]	Partially mRNA Vaccinated (2 doses)[2]	Fully mRNA Vaccinated[3]	Fully Ad26.COV2.S Vaccinated[3]	
B. Emergency Department (ED) and Urgent Care (UC) Visits	N (Col. %)	N (Row %)	N (Row %)	SMD	N (Row %)	N (Row %)	N (Row %)	N (Row %)	N (Row %)	SMD[4]
All ED and UC Visits	21522 (100)	18271 (85)	3251 (15)		11812 (55)	1920 (9)	1269 (6)	6065 (28)	456 (2)	
Events per person				0.09						0.00
First ED/UC event per person	18537 (86)	15822 (85)	2715 (15)		10190 (55)	1688 (9)	1088 (6)	5181 (28)	390 (2)	
Repeat ED/UC event per person	2985 (14)	2449 (82)	536 (18)		1622 (54)	232 (8)	181 (6)	884 (30)	66 (2)	
By medical event setting				0.00						0.14
ED visits	18375 (85)	15598 (85)	2777 (15)		10351 (56)	1582 (9)	1069 (6)	5000 (27)	373 (2)	
UC visits	3147 (15)	2673 (85)	474 (15)		1461 (46)	338 (11)	200 (6)	1065 (34)	83 (3)	
Month of ED/UC event[5]				0.22						0.40
January	353 (2)	237 (67)	116 (33)		335 (95)	16 (5)	1 (0)	1 (0)	0 (0)	
February	2398 (11)	2001 (83)	397 (17)		1732 (72)	374 (16)	196 (8)	96 (4)	0 (0)	
March	4486 (21)	3925 (87)	561 (13)		2655 (59)	610 (14)	418 (9)	775 (17)	28 (1)	
April	5956 (28)	5039 (85)	917 (15)		3049 (51)	523 (9)	433 (7)	1803 (30)	148 (2)	
May	6069 (28)	5142 (85)	927 (15)		2954 (49)	309 (5)	185 (3)	2430 (40)	191 (3)	
June	2260 (11)	1927 (85)	333 (15)		1087 (48)	88 (4)	36 (2)	960 (42)	89 (4)	
Sites				0.31						0.33
Intermountain Healthcare	8993 (42)	7600 (85)	1393 (15)		4612 (51)	908 (10)	557 (6)	2700 (30)	216 (2)	
Kaiser Permanente Northwest	4682 (22)	4277 (91)	405 (9)		2100 (45)	440 (9)	327 (7)	1702 (36)	113 (2)	
Regenstrief Institute	7847 (36)	6394 (81)	1453 (19)		5100 (65)	572 (7)	385 (5)	1663 (21)	127 (2)	
Site-regions				0.47						0.40
Intermountain Healthcare - site-region 1	605 (3)	522 (86)	83 (14)		278 (46)	55 (9)	35 (6)	225 (37)	12 (2)	
Intermountain Healthcare - site-region 2	356 (2)	278 (78)	78 (22)		180 (51)	35 (10)	22 (6)	116 (33)	3 (1)	
Intermountain Healthcare - site-region 3	3266 (15)	2864 (88)	402 (12)		1542 (47)	351 (11)	219 (7)	1073 (33)	81 (2)	
Intermountain Healthcare - site-region 4	1418 (7)	1166 (82)	252 (18)		721 (51)	129 (9)	80 (6)	472 (33)	16 (1)	
Intermountain Healthcare - site-region 5	310 (1)	262 (85)	48 (15)		165 (53)	31 (10)	24 (8)	82 (26)	8 (3)	
Intermountain Healthcare - site-region 6	1146 (5)	983 (86)	163 (14)		623 (54)	111 (10)	72 (6)	307 (27)	33 (3)	
Intermountain Healthcare - site-region 7	283 (1)	241 (85)	42 (15)		159 (56)	27 (10)	15 (5)	77 (27)	5 (2)	

Intermountain Healthcare - site-region 8	1609 (7)	1284 (80)	325 (20)		944 (59)	169 (11)	90 (6)	348 (22)	58 (4)	
Kaiser Permanente Northwest - site-region 1	2197 (10)	2004 (91)	193 (9)		915 (42)	232 (11)	147 (7)	828 (38)	75 (3)	
Kaiser Permanente Northwest - site-region 2	1939 (9)	1794 (93)	145 (7)		916 (47)	155 (8)	144 (7)	697 (36)	27 (1)	
Kaiser Permanente Northwest - site-region 3	546 (3)	479 (88)	67 (12)		269 (49)	53 (10)	36 (7)	177 (32)	11 (2)	
Regenstrief Institute - site-region 1	894 (4)	705 (79)	189 (21)		658 (74)	58 (6)	40 (4)	129 (14)	9 (1)	
Regenstrief Institute - site-region 2	518 (2)	420 (81)	98 (19)		316 (61)	23 (4)	17 (3)	148 (29)	14 (3)	
Regenstrief Institute - site-region 3	291 (1)	156 (54)	135 (46)		216 (74)	27 (9)	16 (5)	30 (10)	2 (1)	
Regenstrief Institute - site-region 4	884 (4)	695 (79)	189 (21)		574 (65)	65 (7)	47 (5)	184 (21)	14 (2)	
Regenstrief Institute - site-region 5	2339 (11)	1968 (84)	371 (16)		1455 (62)	180 (8)	136 (6)	528 (23)	40 (2)	
Regenstrief Institute - site-region 6	639 (3)	530 (83)	109 (17)		445 (70)	49 (8)	30 (5)	107 (17)	8 (1)	
Regenstrief Institute - site-region 7	176 (1)	153 (87)	23 (13)		119 (68)	12 (7)	7 (4)	35 (20)	3 (2)	
Regenstrief Institute - site-region 8	711 (3)	581 (82)	130 (18)		477 (67)	45 (6)	27 (4)	151 (21)	11 (2)	
Regenstrief Institute - site-region 9	398 (2)	344 (86)	54 (14)		233 (59)	37 (9)	20 (5)	101 (25)	7 (2)	
Regenstrief Institute - site-region 10	191 (1)	179 (94)	12 (6)		112 (59)	14 (7)	13 (7)	52 (27)	0 (0)	
Regenstrief Institute - site-region missing	806 (4)	663 (82)	143 (18)		495 (61)	62 (8)	32 (4)	198 (25)	19 (2)	
Age groups				0.35						0.41
50-64 years	7352 (34)	5819 (79)	1533 (21)		4908 (67)	547 (7)	325 (4)	1336 (18)	236 (3)	
65-74 years	6569 (31)	5616 (85)	953 (15)		3518 (54)	611 (9)	403 (6)	1915 (29)	122 (2)	
75-84 years	5235 (24)	4656 (89)	579 (11)		2359 (45)	539 (10)	369 (7)	1893 (36)	75 (1)	
≥85 years	2366 (11)	2180 (92)	186 (8)		1027 (43)	223 (9)	172 (7)	921 (39)	23 (1)	
Race (regardless of ethnicity)				0.18						0.22
White	17564 (82)	15089 (86)	2475 (14)		9334 (53)	1599 (9)	1076 (6)	5182 (30)	373 (2)	
Black	832 (4)	655 (79)	177 (21)		604 (73)	55 (7)	25 (3)	134 (16)	14 (2)	
Other[6]	741 (3)	625 (84)	116 (16)		391 (53)	87 (12)	54 (7)	192 (26)	17 (2)	
Unknown	2385 (11)	1902 (80)	483 (20)		1483 (62)	179 (8)	114 (5)	557 (23)	52 (2)	
Ethnicity (regardless of race)				0.19						0.14
Hispanic	1170 (5)	877 (75)	293 (25)		725 (62)	102 (9)	65 (6)	250 (21)	28 (2)	
Non-Hispanic	18142 (84)	15606 (86)	2536 (14)		9718 (54)	1666 (9)	1105 (6)	5273 (29)	380 (2)	
Unknown	2210 (10)	1788 (81)	422 (19)		1369 (62)	152 (7)	99 (4)	542 (25)	48 (2)	
Underlying respiratory condition at discharge				-0.26						0.09
Chronic respiratory condition[7]	7383 (34)	6598 (89)	785 (11)		3832 (52)	703 (10)	463 (6)	2206 (30)	179 (2)	
None	14139 (66)	11673 (83)	2466 (17)		7980 (56)	1217 (9)	806 (6)	3859 (27)	277 (2)	
Underlying non-respiratory condition at discharge				-0.30						0.18
Chronic non-respiratory condition[8]	12663 (59)	11157 (88)	1506 (12)		6483 (51)	1179 (9)	796 (6)	3947 (31)	258 (2)	

None	8859 (41)	7114 (80)	1745 (20)		5329 (60)	741 (8)	473 (5)	2118 (24)	198 (2)	
COVID-19-like illness (CLI) ICD discharge codes				0.99						-0.15
≥1 CLI clinical diagnosis code[9]	11631 (54)	8740 (75)	2891 (25)		6785 (58)	992 (9)	606 (5)	2992 (26)	256 (2)	
No clinical diagnosis but ≥1 CLI sign or symptom[10]	9891 (46)	9531 (96)	360 (4)		5027 (51)	928 (9)	663 (7)	3073 (31)	200 (2)	
CLI diagnosis and placement among discharge codes				0.78						-0.26
CLI is first or primary diagnosis	11290 (52)	8622 (76)	2668 (24)		6885 (61)	944 (8)	599 (5)	2619 (23)	243 (2)	
CLI is not first or primary diagnosis	10232 (48)	9649 (94)	583 (6)		4927 (48)	976 (10)	670 (7)	3446 (34)	213 (2)	
COVID-19 Vaccinations				0.93						
Unvaccinated	11812 (55)	8965 (76)	2847 (24)		11812 (100)	0 (0)	0 (0)	0 (0)	0 (0)	
BNT162b2 (Pfizer-BioNTech)	5212 (24)	4988 (96)	224 (4)		0 (0)	912 (17)	711 (14)	3589 (69)	0 (0)	
mRNA-1273 (Moderna)	4042 (19)	3891 (96)	151 (4)		0 (0)	1008 (25)	558 (14)	2476 (61)	0 (0)	
Ad26.COV2.S (Johnson & Johnson)	456 (2)	427 (94)	29 (6)		0 (0)	0 (0)	0 (0)	0 (0)	456 (100)	

Table S14 Characteristics of Sample – Positives Only - Hospitalizations

	Total SARS-CoV-2 Positives N (Col. %)	Unvaccinated N (Row %)	Partially mRNA Vaccinated (1 dose)[1] N (Row %)	Partially mRNA Vaccinated (2 doses)[2] N (Row %)	Fully mRNA Vaccinated[3] N (Row %)	Fully Ad26.COV2.S Vaccinated[3] N (Row %)	SMD[4]
A. Hospitalizations							
All hospitalizations	4321 (100)	3695 (86)	231 (5)	107 (2)	258 (6)	30 (1)	
Events per person							0.10
First hospitalization per person	4271 (99)	3662 (86)	225 (5)	105 (2)	251 (6)	28 (1)	
Repeat hospitalization per person	50 (1)	33 (66)	6 (12)	2 (4)	7 (14)	2 (4)	
Month of hospitalization index date[5]							0.35
January	297 (7)	286 (96)	10 (3)	1 (0)	0 (0)	0 (0)	
February	666 (15)	584 (88)	56 (8)	22 (3)	4 (1)	0 (0)	
March	789 (18)	632 (80)	85 (11)	38 (5)	33 (4)	1 (0)	
April	1270 (29)	1086 (86)	56 (4)	35 (3)	81 (6)	12 (1)	
May	1100 (25)	948 (86)	22 (2)	10 (1)	107 (10)	13 (1)	
June	199 (5)	159 (80)	2 (1)	1 (1)	33 (17)	4 (2)	
Sites							0.50
Columbia University	668 (15)	595 (89)	39 (6)	13 (2)	20 (3)	1 (0)	
HealthPartners	61 (1)	47 (77)	8 (13)	1 (2)	5 (8)	0 (0)	
Intermountain Healthcare	557 (13)	471 (85)	31 (6)	16 (3)	35 (6)	4 (1)	
Kaiser Permanente Northern California	665 (15)	488 (73)	47 (7)	24 (4)	96 (14)	2 (0)	
Kaiser Permanente Northwest	118 (3)	98 (83)	10 (8)	4 (3)	4 (3)	2 (2)	
Regenstrief Institute	1661 (38)	1437 (87)	86 (5)	40 (2)	85 (5)	13 (1)	
University of Colorado	591 (14)	559 (95)	10 (2)	9 (2)	13 (2)	0 (0)	
Site-regions							0.58
Columbia University - site-region 1	668 (15)	595 (89)	39 (6)	13 (2)	20 (3)	1 (0)	
HealthPartners - site-region 1	57 (1)	44 (77)	7 (12)	1 (2)	5 (9)	0 (0)	
HealthPartners - site-region 2	4 (0)	3 (75)	1 (25)	0 (0)	0 (0)	0 (0)	
Intermountain Healthcare - site-region 1	29 (1)	26 (90)	1 (3)	1 (3)	0 (0)	1 (3)	
Intermountain Healthcare - site-region 2	34 (1)	30 (88)	1 (3)	0 (0)	3 (9)	0 (0)	
Intermountain Healthcare - site-region 3	181 (4)	146 (81)	15 (8)	4 (2)	14 (8)	2 (1)	
Intermountain Healthcare - site-region 4	91 (2)	75 (82)	4 (4)	3 (3)	9 (10)	0 (0)	
Intermountain Healthcare - site-region 5	9 (0)	8 (89)	0 (0)	1 (11)	0 (0)	0 (0)	

Intermountain Healthcare - site-region 6	68 (2)	56 (82)	3 (4)	4 (6)	5 (7)	0 (0)
Intermountain Healthcare - site-region 7	13 (0)	11 (85)	0 (0)	1 (8)	1 (8)	0 (0)
Intermountain Healthcare - site-region 8	132 (3)	119 (90)	7 (5)	2 (2)	3 (2)	1 (1)
Kaiser Permanente Northern California - site-region 1	54 (1)	35 (65)	7 (13)	3 (6)	8 (15)	1 (2)
Kaiser Permanente Northern California - site-region 2	57 (1)	46 (81)	5 (9)	3 (5)	3 (5)	0 (0)
Kaiser Permanente Northern California - site-region 3	219 (5)	174 (79)	13 (6)	9 (4)	22 (10)	1 (0)
Kaiser Permanente Northern California - site-region 4	182 (4)	127 (70)	14 (8)	5 (3)	32 (18)	4 (2)
Kaiser Permanente Northern California - site-region 5	55 (1)	35 (64)	3 (5)	2 (4)	14 (25)	1 (2)
Kaiser Permanente Northern California - site-region 6	13 (0)	8 (62)	2 (15)	0 (0)	3 (23)	0 (0)
Kaiser Permanente Northern California - site-region 7	24 (1)	16 (67)	2 (8)	1 (4)	4 (17)	1 (4)
Kaiser Permanente Northern California - site-region 8	61 (1)	47 (77)	1 (2)	1 (2)	10 (16)	2 (3)
Kaiser Permanente Northwest - site-region 1	75 (2)	64 (85)	7 (9)	2 (3)	1 (1)	1 (1)
Kaiser Permanente Northwest - site-region 2	32 (1)	25 (78)	3 (9)	1 (3)	2 (6)	1 (3)
Kaiser Permanente Northwest - site-region 3	11 (0)	9 (82)	0 (0)	1 (9)	1 (9)	0 (0)
Regenstrief Institute - site-region 1	411 (10)	370 (90)	22 (5)	7 (2)	12 (3)	0 (0)
Regenstrief Institute - site-region 2	107 (2)	87 (81)	11 (10)	2 (2)	5 (5)	2 (2)
Regenstrief Institute - site-region 3	48 (1)	43 (90)	3 (6)	0 (0)	2 (4)	0 (0)
Regenstrief Institute - site-region 4	155 (4)	139 (90)	5 (3)	3 (2)	7 (5)	1 (1)
Regenstrief Institute - site-region 5	420 (10)	366 (87)	14 (3)	11 (3)	23 (5)	6 (1)
Regenstrief Institute - site-region 6	160 (4)	133 (83)	8 (5)	5 (3)	13 (8)	1 (1)
Regenstrief Institute - site-region 7	6 (0)	6 (100)	0 (0)	0 (0)	0 (0)	0 (0)
Regenstrief Institute - site-region 8	121 (3)	102 (84)	8 (7)	4 (3)	6 (5)	1 (1)
Regenstrief Institute - site-region 9	67 (2)	51 (76)	9 (13)	1 (1)	6 (9)	0 (0)
Regenstrief Institute - site-region 10	15 (0)	13 (87)	1 (7)	1 (7)	0 (0)	0 (0)
Regenstrief Institute - site-region missing	151 (3)	127 (84)	5 (3)	6 (4)	11 (7)	2 (1)
University of Colorado - site-region 1	172 (4)	157 (91)	3 (2)	3 (2)	9 (5)	0 (0)
University of Colorado - site-region 2	208 (5)	196 (94)	6 (3)	3 (1)	3 (1)	0 (0)
University of Colorado - site-region 3	211 (5)	206 (98)	1 (0)	3 (1)	1 (0)	0 (0)
Age groups						0.44
50-64 years	1328 (31)	1219 (92)	41 (3)	20 (2)	33 (2)	15 (1)
65-74 years	1319 (31)	1142 (87)	75 (6)	26 (2)	68 (5)	8 (1)
75-84 years	1089 (25)	887 (81)	74 (7)	34 (3)	89 (8)	5 (0)
≥85 years	585 (14)	447 (76)	41 (7)	27 (5)	68 (12)	2 (0)
Race (regardless of ethnicity)						0.17
White	2662 (62)	2255 (85)	140 (5)	73 (3)	175 (7)	19 (1)
Black	488 (11)	436 (89)	21 (4)	7 (1)	20 (4)	4 (1)
Other[6]	200 (5)	158 (79)	12 (6)	10 (5)	19 (10)	1 (1)

Unknown	971 (22)	846 (87)	58 (6)	17 (2)	44 (5)	6 (1)	
Ethnicity (regardless of race)							0.09
Hispanic	749 (17)	656 (88)	36 (5)	16 (2)	35 (5)	6 (1)	
Non-Hispanic	2879 (67)	2460 (85)	144 (5)	77 (3)	179 (6)	19 (1)	
Unknown	693 (16)	579 (84)	51 (7)	14 (2)	44 (6)	5 (1)	
Underlying respiratory condition at discharge							-0.08
Chronic respiratory condition7	2734 (63)	2359 (86)	140 (5)	62 (2)	152 (6)	21 (1)	
None	1587 (37)	1336 (84)	91 (6)	45 (3)	106 (7)	9 (1)	
Underlying non-respiratory condition at discharge							0.24
Chronic non-respiratory condition8	3610 (84)	3043 (84)	201 (6)	97 (3)	240 (7)	29 (1)	
None	711 (16)	652 (92)	30 (4)	10 (1)	18 (3)	1 (0)	
COVID-19-like illness (CLI) ICD discharge codes							-0.12
≥1 CLI clinical diagnosis code9	4235 (98)	3632 (86)	222 (5)	104 (2)	248 (6)	29 (1)	
No clinical diagnosis but ≥1 CLI sign or symptom[10]	86 (2)	63 (73)	9 (10)	3 (3)	10 (12)	1 (1)	
CLI diagnosis and placement among discharge codes							-0.35
CLI is first or primary diagnosis	2694 (62)	2395 (89)	121 (4)	57 (2)	108 (4)	13 (0)	
CLI is not first or primary diagnosis	1627 (38)	1300 (80)	110 (7)	50 (3)	150 (9)	17 (1)	
Intensive care unit (ICU) admissions							-0.09
Admitted to ICU	788 (18)	692 (88)	39 (5)	15 (2)	38 (5)	4 (1)	
Not in ICU during hospitalization	3533 (82)	3003 (85)	192 (5)	92 (3)	220 (6)	26 (1)	
COVID-19 Vaccinations							
Unvaccinated	3695 (86)	3695 (100)	0 (0)	0 (0)	0 (0)	0 (0)	
BNT162b2 (Pfizer-BioNTech)	360 (8)	0 (0)	140 (39)	57 (16)	163 (45)	0 (0)	
mRNA-1273 (Moderna)	236 (5)	0 (0)	91 (39)	50 (21)	95 (40)	0 (0)	
Ad26.COV2.S (Johnson & Johnson)	30 (1)	0 (0)	0 (0)	0 (0)	0 (0)	30 (100)	

Note: All patients with indeterminate immunization status (receipt of dose-1 of mRNA vaccine 1-13 days prior to index test date) were excluded from table.

Abbreviations: Standard Mean Difference (SMD), COVID-like Illness (CLI), International Classification of Disease (ICD), Intensive Care Unit (ICU), Emergency Department (ED), Urgent Care (UC)

[1]Partially vaccinated with 1 dose: patients received dose-1 of mRNA vaccine ≥ 14 days prior to the index text date, had not received dose-2 by the index test date.

[2]Partially vaccinated with 2 doses: patients received dose-1 and dose-2 of mRNA vaccine, dose-2 receipt date 1-13 days prior to index date.

[3]Fully vaccinated: patients received single dose of J&J vaccine, dose-1 and dose-2 of mRNA vaccine, dose-2 of mRNA vaccine ≥ 14 days prior to the index text date.

[4]Standard Mean Difference (SMD) calculation compares unvaccinated to any receipt of vaccine (partial dose-1, partial dose-2 and full vaccination).

[5]Index date for each medical encounter was defined as the date of respiratory specimen collection associated with the most recent positive or negative SARS-CoV-2 test result prior to the medical encounter or the date of the medical encounter if testing only occurred after the admission or encounter date.

[6]Other race include Asian, Hawaiian or Other Pacific islander, American Indian or Alaskan Native, Other not-listed and multi-race.

[7]Underlying chronic respiratory conditions include asthma, chronic obstructive pulmonary disease (COPD), other lung disease.

[8]Underlying chronic non-respiratory conditions include heart failure, ischemic heart disease, hypertension, other heart disease, stroke, other cerebrovascular disease, diabetes (type 1, 2 and due to other specified conditions), other metabolic disease, clinical obesity, clinically underweight, renal disease, liver disease, blood disorder, other immunosuppressive conditions, organ transplant recipient, cancer, dementia, neurological/musculoskeletal disorder or Down's syndrome.

[9]CLI clinical discharge diagnosis codes include: COVID-19 U codes, COVID-19 pneumonia, influenza pneumonia, other viral pneumonia, pneumonia and influenza (bacterial and other) influenza disease, acute respiratory distress syndrome (ARDS), COPD exacerbation, asthma exacerbation, respiratory failure, other acute lower respiratory tract infection, sinusitis, acute upper respiratory tract infection.

[10]CLI signs and symptoms include: hemoptysis, cough, dyspnea unspecified, chest pain or breathing/painful respiration, asphyxia, hypoxemia, pleurisy, respiratory arrest, abnormal sputum, other specified symptoms and signs involving the circulatory and respiratory systems, fever, chills (without fever), diarrhea, disturbance of taste or smell, headache, myalgia, sepsis, other malaise, other fatigue, shock (unspecified), debility (unspecified), altered level of consciousness/mental state, weakness, nausea and vomiting, rash or other nonspecific skin eruption, abdominal pain

Table S15. Characteristics of Sample – Positives Only - ED/UC

	Total SARS-CoV-2 Positives N (Col. %)	**Unvaccinated** N (Row %)	**Partially mRNA Vaccinated (1 dose)[1]** N (Row %)	**Partially mRNA Vaccinated (2 doses)[2]** N (Row %)	**Fully mRNA Vaccinated[3]** N (Row %)	**Fully Ad26.COV2.S Vaccinated[3]** N (Row %)	SMD[4]
B. Emergency Department (ED) and Urgent Care (UC) Visits							
All ED and UC Visits	3251 (100)	2847 (88)	155 (5)	66 (2)	154 (5)	29 (1)	
Events per person							-0.03
First ED/UC event per person	2715 (84)	2374 (87)	135 (5)	57 (2)	125 (5)	24 (1)	
Repeat ED/UC event per person	536 (16)	473 (88)	20 (4)	9 (2)	29 (5)	5 (1)	
By medical event setting							0.15
ED visits	2777 (85)	2451 (88)	128 (5)	55 (2)	120 (4)	23 (1)	
UC visits	474 (15)	396 (84)	27 (6)	11 (2)	34 (7)	6 (1)	
Month of ED/UC event[5]							0.29
January	116 (4)	112 (97)	4 (3)	0 (0)	0 (0)	0 (0)	
February	397 (12)	344 (87)	32 (8)	15 (4)	6 (2)	0 (0)	
March	561 (17)	473 (84)	48 (9)	19 (3)	19 (3)	2 (0)	
April	917 (28)	803 (88)	47 (5)	21 (2)	37 (4)	9 (1)	
May	927 (29)	839 (91)	21 (2)	4 (0)	52 (6)	11 (1)	
June	333 (10)	276 (83)	3 (1)	7 (2)	40 (12)	7 (2)	
Sites							0.19
Intermountain Healthcare	1393 (43)	1193 (86)	66 (5)	31 (2)	90 (6)	13 (1)	
Kaiser Permanente Northwest	405 (12)	354 (87)	21 (5)	10 (2)	16 (4)	4 (1)	
Regenstrief Institute	1453 (45)	1300 (89)	68 (5)	25 (2)	48 (3)	12 (1)	
Site-regions							0.35
Intermountain Healthcare - site-region 1	83 (3)	76 (92)	3 (4)	0 (0)	4 (5)	0 (0)	
Intermountain Healthcare - site-region 2	78 (2)	57 (73)	6 (8)	3 (4)	12 (15)	0 (0)	
Intermountain Healthcare - site-region 3	402 (12)	334 (83)	23 (6)	8 (2)	28 (7)	9 (2)	
Intermountain Healthcare - site-region 4	252 (8)	215 (85)	11 (4)	7 (3)	19 (8)	0 (0)	

Intermountain Healthcare - site-region 5	48 (1)	44 (92)	1 (2)	2 (4)	1 (2)	0 (0)	
Intermountain Healthcare - site-region 6	163 (5)	133 (82)	7 (4)	7 (4)	15 (9)	1 (1)	
Intermountain Healthcare - site-region 7	42 (1)	39 (93)	0 (0)	1 (2)	2 (5)	0 (0)	
Intermountain Healthcare - site-region 8	325 (10)	295 (91)	15 (5)	3 (1)	9 (3)	3 (1)	
Kaiser Permanente Northwest - site-region 1	193 (6)	169 (88)	13 (7)	4 (2)	6 (3)	1 (1)	
Kaiser Permanente Northwest - site-region 2	145 (4)	126 (87)	7 (5)	3 (2)	8 (6)	1 (1)	
Kaiser Permanente Northwest - site-region 3	67 (2)	59 (88)	1 (1)	3 (4)	2 (3)	2 (3)	
Regenstrief Institute - site-region 1	189 (6)	169 (89)	10 (5)	4 (2)	5 (3)	1 (1)	
Regenstrief Institute - site-region 2	98 (3)	88 (90)	4 (4)	2 (2)	2 (2)	2 (2)	
Regenstrief Institute - site-region 3	135 (4)	116 (86)	12 (9)	3 (2)	4 (3)	0 (0)	
Regenstrief Institute - site-region 4	189 (6)	167 (88)	7 (4)	3 (2)	9 (5)	3 (2)	
Regenstrief Institute - site-region 5	371 (11)	339 (91)	15 (4)	9 (2)	6 (2)	2 (1)	
Regenstrief Institute - site-region 6	109 (3)	102 (94)	3 (3)	1 (1)	3 (3)	0 (0)	
Regenstrief Institute - site-region 7	23 (1)	19 (83)	3 (13)	1 (4)	0 (0)	0 (0)	
Regenstrief Institute - site-region 8	130 (4)	113 (87)	5 (4)	1 (1)	9 (7)	2 (2)	
Regenstrief Institute - site-region 9	54 (2)	47 (87)	5 (9)	0 (0)	1 (2)	1 (2)	
Regenstrief Institute - site-region 10	12 (0)	11 (92)	0 (0)	0 (0)	1 (8)	0 (0)	
Regenstrief Institute - site-region missing	143 (4)	129 (90)	4 (3)	1 (1)	8 (6)	1 (1)	
Age groups							0.50
50-64 years	1533 (47)	1416 (92)	50 (3)	13 (1)	35 (2)	19 (1)	
65-74 years	953 (29)	829 (87)	47 (5)	22 (2)	48 (5)	7 (1)	
75-84 years	579 (18)	459 (79)	45 (8)	21 (4)	51 (9)	3 (1)	
≥85 years	186 (6)	143 (77)	13 (7)	10 (5)	20 (11)	0 (0)	
Race (regardless of ethnicity)							0.15
White	2475 (76)	2158 (87)	114 (5)	53 (2)	128 (5)	22 (1)	
Black	177 (5)	166 (94)	7 (4)	1 (1)	3 (2)	0 (0)	
Other[6]	116 (4)	99 (85)	7 (6)	5 (4)	4 (3)	1 (1)	
Unknown	483 (15)	424 (88)	27 (6)	7 (1)	19 (4)	6 (1)	
Ethnicity (regardless of race)							0.07
Hispanic	293 (9)	248 (85)	14 (5)	5 (2)	23 (8)	3 (1)	
Non-Hispanic	2536 (78)	2224 (88)	120 (5)	53 (2)	118 (5)	21 (1)	
Unknown	422 (13)	375 (89)	21 (5)	8 (2)	13 (3)	5 (1)	
Underlying respiratory condition at discharge							0.07
Chronic respiratory condition[7]	785 (24)	677 (86)	36 (5)	20 (3)	44 (6)	8 (1)	
None	2466 (76)	2170 (88)	119 (5)	46 (2)	110 (4)	21 (1)	

Underlying non-respiratory condition at discharge							0.15
Chronic non-respiratory condition[8]	1506 (46)	1293 (86)	67 (4)	33 (2)	98 (7)	15 (1)	
None	1745 (54)	1554 (89)	88 (5)	33 (2)	56 (3)	14 (1)	
COVID-19-like illness (CLI) ICD discharge codes							-0.08
≥1 CLI clinical diagnosis code[9]	2891 (89)	2541 (88)	136 (5)	54 (2)	135 (5)	25 (1)	
No clinical diagnosis but ≥1 CLI sign or symptom[10]	360 (11)	306 (85)	19 (5)	12 (3)	19 (5)	4 (1)	
CLI diagnosis and placement among discharge codes							-0.20
CLI is first or primary diagnosis	2668 (82)	2365 (89)	122 (5)	46 (2)	109 (4)	26 (1)	
CLI is not first or primary diagnosis	583 (18)	482 (83)	33 (6)	20 (3)	45 (8)	3 (1)	
COVID-19 Vaccinations							
Unvaccinated	2847 (88)	2847 (100)	0 (0)	0 (0)	0 (0)	0 (0)	
BNT162b2 (Pfizer-BioNTech)	224 (7)	0 (0)	88 (39)	31 (14)	105 (47)	0 (0)	
mRNA-1273 (Moderna)	151 (5)	0 (0)	67 (44)	35 (23)	49 (32)	0 (0)	
Ad26.COV2.S (Johnson & Johnson)	29 (1)	0 (0)	0 (0)	0 (0)	0 (0)	29 (100)	

Note: All patients with indeterminate immunization status (receipt of dose-1 of mRNA vaccine 1-13 days prior to index test date) were excluded from table.

Abbreviations: Standard Mean Difference (SMD), COVID-like Illness (CLI), International Classification of Disease (ICD), Intensive Care Unit (ICU), Emergency Department (ED), Urgent Care (UC)

[1]Partially vaccinated with 1 dose: patients received dose-1 of mRNA vaccine ≥ 14 days prior to the index text date, had not received dose-2 by the index test date.

[2]Partially vaccinated with 2 doses: patients received dose-1 and dose-2 of mRNA vaccine, dose-2 receipt date 1-13 days prior to index date.

[3]Fully vaccinated: patients received single dose of J&J vaccine, dose-1 and dose-2 of mRNA vaccine, dose-2 of mRNA vaccine ≥ 14 days prior to the index text date.

[4]Standard Mean Difference (SMD) calculation compares unvaccinated to any receipt of vaccine (partial dose-1, partial dose-2 and full vaccination).

[5]Index date for each medical encounter was defined as the date of respiratory specimen collection associated with the most recent positive or negative SARS-CoV-2 test result prior to the medical encounter or the date of the medical encounter if testing only occurred after the admission or encounter date.

[6]Other race include Asian, Hawaiian or Other Pacific islander, American Indian or Alaskan Native, Other not-listed and multi-race.

[7]Underlying chronic respiratory conditions include asthma, chronic obstructive pulmonary disease (COPD), other lung disease.

[8]Underlying chronic non-respiratory conditions include heart failure, ischemic heart disease, hypertension, other heart disease, stroke, other cerebrovascular disease, diabetes (type 1, 2 and due to other specified conditions), other metabolic disease, clinical obesity, clinically underweight, renal disease, liver disease, blood disorder, other immunosuppressive conditions, organ transplant recipient, cancer, dementia, neurological/musculoskeletal disorder or Down's syndrome.

[9]CLI clinical discharge diagnosis codes include: COVID-19 U codes, COVID-19 pneumonia, influenza pneumonia, other viral pneumonia, pneumonia and influenza (bacterial and other), influenza disease, acute respiratory distress syndrome (ARDS), COPD exacerbation, asthma exacerbation, respiratory failure, other acute lower respiratory tract infection, sinusitis, acute upper respiratory tract infection.

[10]CLI signs and symptoms include: hemoptysis, cough, dyspnea unspecified, chest pain or breathing/painful respiration, asphyxia, hypoxemia, pleurisy, respiratory arrest, abnormal sputum, other specified symptoms and signs involving the circulatory and respiratory systems, fever, chills (without fever), diarrhea, disturbance of taste or smell, headache, myalgia, sepsis, other malaise, other fatigue, shock (unspecified), debility (unspecified), altered level of consciousness/mental state, weakness, nausea and vomiting, rash or other nonspecific skin eruption, abdominal pain

Table S16. Full listing of all estimates of messenger RNA (mRNA) vaccine effectiveness (VE) among COVID-19-associated hospitalizations and intensive care unit (ICU) admissions events

					VE before Adjusted Model					VE[1]				
	Total	SARS-CoV-2 Positive	(	Row %	)	%	(	95% CI	)	%	(	95% CI	)	
mRNA VE among COVID-19 hospitalizations														
VE COVID-19 vaccines (aged ≥50 years)														
Unvaccinated (Referent)	20406	3695	(	18.1	)									
Partially 1-Dose Vaccinated	3083	231	(	7.5	)	63	(	58 - 68	)	54	(	47 - 61	)	
Partially 2-Dose Vaccinated	2482	107	(	4.3	)	80	(	75 - 83	)	73	(	66 - 79	)	
Full 2-dose mRNA Vaccinated	14874	258	(	1.7	)	92	(	91 - 93	)	89	(	87 - 91	)	
By mRNA vaccine product among COVID-19 hospitalizations														
VE of BioNTech-Pfizer mRNA (aged ≥50 years)														
Unvaccinated (Referent)	20406	3695	(	18.1	)									
Partially 1-Dose Vaccinated	1444	140	(	9.7	)	51	(	42 - 60	)	33	(	18 - 46	)	
Partially 2-Dose Vaccinated	1348	57	(	4.2	)	80	(	74 - 85	)	73	(	63 - 81	)	
Fully Vaccinated	8500	163	(	1.9	)	91	(	90 - 92	)	87	(	85 - 90	)	
VE of Moderna mRNA (aged ≥50 years)														
Unvaccinated (Referent)	20406	3695	(	18.1	)									
Partially 1-Dose Vaccinated	1639	91	(	5.6	)	73	(	67 - 79	)	68	(	59 - 75	)	
Partially 2-Dose Vaccinated	1134	50	(	4.4	)	79	(	73 - 85	)	74	(	64 - 82	)	
Fully Vaccinated	6374	95	(	1.5	)	93	(	92 - 94	)	91	(	89 - 93	)	
Ad26.COV2.S (Johnson & Johnson)														
Unvaccinated (Referent)	10761	2006	(	18.6	)									
Full 1-dose Vaccinated [2]	707	30	(	4.2	)	81	(	73 - 87	)	68	(	50 - 79	)	
By Age Group among COVID-19 hospitalizations														
VE mRNA vaccines (aged 50-64 years)														
Unvaccinated (Referent)	5532	1219	(	22.0	)									
Partially 1-Dose Vaccinated	585	41	(	7.0	)	73	(	64 - 81	)	68	(	53 - 77	)	
Partially 2-Dose Vaccinated	467	20	(	4.3	)	84	(	76 - 90	)	82	(	70 - 89	)	
Fully Vaccinated	1898	33	(	1.7	)	94	(	91 - 96	)	93	(	89 - 95	)	
VE mRNA vaccines (aged 65-74 years)														

Unvaccinated (Referent)	6681	1142	(	17.1	)									
Partially 1-Dose Vaccinated	1014	75	(	7.4	)	61	(	51	-	70	)	54	(	40	-	65	)
Partially 2-Dose Vaccinated	795	26	(	3.3	)	84	(	76	-	89	)	79	(	65	-	87	)
Fully Vaccinated	4481	68	(	1.5	)	93	(	91	-	94	)	90	(	86	-	92	)
VE mRNA vaccines (aged 75-84 years)																	
Unvaccinated (Referent)	5233	887	(	17.0	)									
Partially 1-Dose Vaccinated	935	74	(	7.9	)	58	(	46	-	67	)	43	(	24	-	58	)
Partially 2-Dose Vaccinated	772	34	(	4.4	)	77	(	68	-	84	)	70	(	56	-	80	)
Fully Vaccinated	5189	89	(	1.7	)	91	(	89	-	93	)	88	(	84	-	90	)
VE mRNA vaccines (aged ≥85 years)																	
Unvaccinated (Referent)	2960	447	(	15.1	)									
Partially 1-Dose Vaccinated	549	41	(	7.5	)	55	(	37	-	68	)	38	(	11	-	57	)
Partially 2-Dose Vaccinated	448	27	(	6.0	)	64	(	47	-	76	)	56	(	32	-	72	)
Fully Vaccinated	3306	68	(	2.1	)	88	(	85	-	91	)	83	(	77	-	87	)
<u>By Race (regardless of ethnicity) among COVID-19 hospitalizations</u>																	
VE mRNA vaccines among Black adults aged ≥50 years																	
Unvaccinated (Referent)	2393	436	(	18.2	)									
Partially 1-Dose Vaccinated	269	21	(	7.8	)	62	(	41	-	77	)	47	(	10	-	69	)
Partially 2-Dose Vaccinated	194	7	(	3.6	)	83	(	67	-	93	)	75	(	36	-	90	)
Fully Vaccinated	961	20	(	2.1	)	90	(	85	-	94	)	86	(	75	-	92	)
VE mRNA vaccines among white adults aged ≥50 years																	
Unvaccinated (Referent)	13886	2255	(	16.2	)									
Partially 1-Dose Vaccinated	2246	140	(	6.2	)	66	(	59	-	71	)	57	(	48	-	65	)
Partially 2-Dose Vaccinated	1779	73	(	4.1	)	78	(	72	-	83	)	71	(	61	-	78	)
Fully Vaccinated	10655	175	(	1.6	)	91	(	90	-	93	)	90	(	88	-	91	)
VE mRNA vaccines among other (Asian, Hawaiian or Other Pacific Islander, American Indian or Alaska Native, Multi-racial, or Other) adults aged ≥50 years																	
Unvaccinated (Referent)	913	158	(	17.3	)									
Partially 1-Dose Vaccinated	183	12	(	6.6	)	66	(	41	-	83	)	57	(	9	-	79	)
Partially 2-Dose Vaccinated	223	10	(	4.5	)	78	(	59	-	89	)	63	(	23	-	82	)
Fully Vaccinated	1496	19	(	1.3	)	94	(	90	-	96	)	92	(	86	-	95	)

By Ethnicity (regardless of race) among COVID-19 hospitalizations															
VE mRNA vaccines among Hispanic adults aged ≥50 years															
Unvaccinated (Referent)	2376	656	(	27.6	)										
Partially 1-Dose Vaccinated	307	36	(	11.7	)	65	(	51	-	76	)	56	(	35	-	70	)
Partially 2-Dose Vaccinated	264	16	(	6.1	)	83	(	73	-	90	)	80	(	63	-	89	)
Fully Vaccinated	1540	35	(	2.3	)	94	(	92	-	96	)	90	(	85	-	93	)
VE mRNA vaccines among non-Hispanic adults aged ≥50 years															
Unvaccinated (Referent)	15361	2460	(	16.0	)										
Partially 1-Dose Vaccinated	2318	144	(	6.2	)	65	(	59	-	71	)	57	(	48	-	65	)
Partially 2-Dose Vaccinated	1863	77	(	4.1	)	77	(	72	-	82	)	71	(	62	-	78	)
Fully Vaccinated	11067	179	(	1.6	)	91	(	90	-	93	)	89	(	87	-	91	)
By Presence or Absence of Underlying Chronic Medical Conditions Associated with Increased Risk of Severe Respiratory Disease															
VE mRNA vaccines among aged ≥50 years with no chronic condition															
Unvaccinated (Referent)	1493	422	(	28.3	)										
Partially 1-Dose Vaccinated	154	21	(	13.6	)	60	(	37	-	76	)	46	(	7	-	69	)
Partially 2-Dose Vaccinated	126	9	(	7.1	)	80	(	63	-	91	)	78	(	52	-	90	)
Fully Vaccinated	565	14	(	2.5	)	94	(	89	-	96	)	92	(	86	-	96	)
VE mRNA vaccines among aged ≥50 years with ≥1 chronic respiratory condition															
Unvaccinated (Referent)	13018	2359	(	18.1	)										
Partially 1-Dose Vaccinated	2033	140	(	6.9	)	67	(	60	-	72	)	56	(	47	-	64	)
Partially 2-Dose Vaccinated	1634	62	(	3.8	)	82	(	77	-	86	)	76	(	68	-	82	)
Fully Vaccinated	10257	152	(	1.5	)	93	(	92	-	94	)	90	(	88	-	92	)
VE mRNA vaccines among aged ≥50 years with ≥1 chronic non-respiratory condition															
Unvaccinated (Referent)	18089	3043	(	16.8	)										
Partially 1-Dose Vaccinated	2835	201	(	7.1	)	62	(	56	-	68	)	54	(	45	-	61	)
Partially 2-Dose Vaccinated	2302	97	(	4.2	)	78	(	73	-	82	)	71	(	62	-	77	)
Fully Vaccinated	13999	240	(	1.7	)	91	(	90	-	92	)	88	(	86	-	90	)

By Alternative Clinical Outcomes																
VE mRNA vaccines among aged ≥50 years with acute respiratory illness diagnosis																
Unvaccinated (Referent)	14805	3632	(	24.5	)											
Partially 1-Dose Vaccinated	2191	222	(	10.1	)	65	(	60	-	70	)	54	(	45	-	61	)
Partially 2-Dose Vaccinated	1748	104	(	5.9	)	81	(	76	-	84	)	74	(	67	-	79	)
Fully Vaccinated	10686	248	(	2.3	)	93	(	92	-	94	)	89	(	88	-	91	)
VE mRNA vaccines among aged ≥50 years with clinical pneumonia diagnosis																
Unvaccinated (Referent)	5491	2324	(	42.3	)											
Partially 1-Dose Vaccinated	624	133	(	21.3	)	63	(	55	-	70	)	49	(	36	-	60	)
Partially 2-Dose Vaccinated	463	40	(	8.6	)	87	(	82	-	91	)	80	(	71	-	86	)
Fully Vaccinated	2555	108	(	4.2	)	94	(	93	-	95	)	92	(	90	-	94	)
VE mRNA vaccines among aged ≥50 years with CLI/signs and symptoms as primary discharge code																
Unvaccinated (Referent)	13022	1942	(	14.9	)											
Partially 1-Dose Vaccinated	1863	131	(	7.0	)	57	(	48	-	64	)	45	(	33	-	56	)
Partially 2-Dose Vaccinated	1449	63	(	4.3	)	74	(	67	-	80	)	68	(	57	-	77	)
Fully Vaccinated	8094	119	(	1.5	)	91	(	90	-	93	)	88	(	86	-	91	)
Among ICU Admissions																
VE mRNA vaccines																
Unvaccinated (Referent)	4024	692	(	17.2	)											
Partially 1-Dose Vaccinated	512	39	(	7.6	)	60	(	45	-	72	)	56	(	35	-	70	)
Partially 2-Dose Vaccinated	388	15	(	3.9	)	81	(	69	-	89	)	75	(	58	-	86	)
Fully Vaccinated	2359	38	(	1.6	)	92	(	89	-	94	)	90	(	86	-	93	)

[1]Adjusted model using inverse propensity weights, calculated using strata specific data, in regression doubly accounting for calendar time, daily virus circulation, age, and geographic cluster.

[2]Variables that did not achieve SMD < 0.2 after propensity weighting and were included as covariates in the model were Admitting Hospital Type and Urban-Rural Classification of Facility

Table S17. Messenger RNA (mRNA) vaccine effectiveness (VE) against COVID-19-associated hospitalizations and emergency department and urgent care (ED/UC) medical events by study site

	IH	KPNC	RG	UCO	CUIMC	KPNW
	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)
mRNA VE among COVID-19 hospitalizations						
VE both mRNA vaccines						
Unvaccinated (Referent)						
Partially 1-Dose Vaccinated	67 (50 - 79)	66 (53 - 75)	46 (30 - 59)	69 (38 - 84)	3 (-46 - 35)	39 (-28 - 71)
Partially 2-Dose Vaccinated	74 (55 - 86)	83 (73 - 89)	69 (55 - 79)	64 (26 - 83)	74 (48 - 87)	68 (-5 - 90)
Fully Vaccinated	91 (86 - 94)	91 (88 - 93)	87 (84 - 90)	89 (79 - 94)	82 (70 - 90)	97 (91 - 99)
mRNA VE among COVID-19 ED/UC						
VE both mRNA vaccines						
Unvaccinated (Referent)						
Partially 1-Dose Vaccinated	72 (63 - 79)		60 (46 - 70)			74 (56 - 84)
Partially 2-Dose Vaccinated	77 (65 - 85)		81 (71 - 88)			80 (55 - 91)
Fully Vaccinated	89 (86 - 91)		90 (85 - 93)			97 (94 - 98)

Legend: A separate model for Health Partners was not calculated because the sample size was not sufficient to calculate a stratified propensity to be vaccinated score.

CUIMC: Columbia University Irving Medical Center
HP: HealthPartners
IH: Intermountain Healthcare
KPNC: Kaiser Permanente Northern California
KPNW: Kaiser Permanente Northwest
RG: Regenstrief Institute
UCO: University of Colorado

Table S18. Full listing of all estimates of messenger RNA (mRNA) vaccine effectiveness (VE) among COVID-19-associated hospitalization by days past most recent dose

					VE before Adjusted Model					VE[1]				
	Total	SARS-CoV-2 Positive	(	Row %)	%	(	95% CI	)		%	(	95% CI	)	
mRNA VE against COVID-19 hospitalizations														
VE COVID-19 vaccines (aged ≥50 years)														
Unvaccinated (Referent)	20618	3711	(	18)										
Indeterminate Vaccination (0-13 days post dose-1)	1751	290	(	17)	10	(	-3	-	21)	-4	(	-21	-	10)
Partially 1-Dose Vaccinated (14-27 days post dose-1)	1895	181	(	10)	52	(	44	-	59)	44	(	33	-	53)
Partially 1-Dose Vaccinated (28-41 days post dose-1)	479	30	(	6)	70	(	57	-	79)	70	(	56	-	80)
Partially 1-Dose Vaccinated (42-55 days post dose-1)	189	4	(	2)	90	(	77	-	97)	91	(	74	-	97)
Partially 1-Dose Vaccinated (≥56 days post dose-1)	561	17	(	3)	86	(	78	-	92)	83	(	71	-	90)
Partially 2-Dose Vaccinated (0-13 days post dose-2)	2497	107	(	4)	80	(	75	-	83)	74	(	67	-	79)
Fully Vaccinated (14-27 days post dose-2)	2754	48	(	2)	92	(	89	-	94)	88	(	84	-	92)
Fully Vaccinated (28-41 days post dose-2)	2783	41	(	1)	93	(	91	-	95)	92	(	88	-	94)
Fully Vaccinated (42-55 days post dose-2)	2603	41	(	2)	93	(	90	-	95)	90	(	87	-	93)
Fully Vaccinated (56-69 days post dose-2)	2394	51	(	2)	90	(	87	-	93)	86	(	82	-	90)
Fully Vaccinated (70-83 days post dose-2)	2048	24	(	1)	95	(	92	-	96)	93	(	89	-	95)
Fully Vaccinated (84-97 days post dose-2)	1528	27	(	2)	92	(	88	-	95)	86	(	79	-	91)
Fully Vaccinated (98-111 days post dose-2)	971	23	(	2)	89	(	84	-	93)	82	(	72	-	89)
Fully Vaccinated (≥112 days post dose-2)	568	11	(	2)	91	(	84	-	95)	86	(	74	-	93)
By mRNA vaccine product against COVID-19 hospitalizations														
VE of BioNTech-Pfizer mRNA (aged ≥50 years)														
Unvaccinated (Referent)	20618	3711	(	18)										
Indeterminate Vaccination (0-13 days post dose-1)	976	163	(	17)	9	(	-8	-	23)	-3	(	-26	-	15)
Partially 1-Dose Vaccinated (14-27 days post dose-1)	939	112	(	12)	38	(	25	-	50)	26	(	7	-	41)
Partially 1-Dose Vaccinated (28-41 days post dose-1)	168	17	(	10)	49	(	18	-	70)	47	(	7	-	70)
Partially 1-Dose Vaccinated (42-55 days post dose-1)	79	3	(	4)	82	(	52	-	96)	80	(	32	-	94)
Partially 1-Dose Vaccinated (≥56 days post dose-1)	283	8	(	3)	87	(	75	-	94)	86	(	69	-	93)
Partially 2-Dose Vaccinated (0-13 days post dose-2)	1357	57	(	4)	80	(	74	-	85)	73	(	63	-	80)
Fully Vaccinated (14-27 days post dose-2)	1586	33	(	2)	90	(	87	-	93)	87	(	80	-	91)
Fully Vaccinated (28-41 days post dose-2)	1572	17	(	1)	95	(	92	-	97)	95	(	91	-	97)
Fully Vaccinated (42-55 days post dose-2)	1456	28	(	2)	91	(	87	-	94)	86	(	79	-	91)
Fully Vaccinated (56-69 days post dose-2)	1365	32	(	2)	89	(	85	-	92)	83	(	75	-	89)

Fully Vaccinated (70-83 days post dose-2)	1184	17	(	1	)	93	(	90	-	96	)	90	(	82	-	94	)
Fully Vaccinated (84-97 days post dose-2)	863	12	(	1	)	94	(	89	-	97	)	87	(	76	-	93	)
Fully Vaccinated (98-111 days post dose-2)	560	18	(	3	)	85	(	77	-	91	)	75	(	57	-	85	)
Fully Vaccinated (≥112 days post dose-2)	362	9	(	2	)	88	(	79	-	94	)	83	(	64	-	92	)
VE of Moderna mRNA (aged ≥50 years)																	
Unvaccinated (Referent)	20618	3711	(| 18 |)												
Indeterminate Vaccination (0-13 days post dose-1)	775	127	(	16	)	11	(	-8	-	27	)	-12	(	-41	-	11	)
Partially 1-Dose Vaccinated (14-27 days post dose-1)	956	69	(	7	)	65	(	55	-	73	)	58	(	44	-	69	)
Partially 1-Dose Vaccinated (28-41 days post dose-1)	311	13	(	4	)	80	(	67	-	89	)	81	(	65	-	90	)
Partially 1-Dose Vaccinated (42-55 days post dose-1)	110	1	(	1	)	96	(	81	-	100	)	98	(	82	-	100	)
Partially 1-Dose Vaccinated (≥56 days post dose-1)	280	9	(	3	)	85	(	72	-	93	)	80	(	54	-	91	)
Partially 2-Dose Vaccinated (0-13 days post dose-2)	1140	50	(	4	)	79	(	73	-	84	)	74	(	63	-	81	)
Fully Vaccinated (14-27 days post dose-2)	1168	15	(	1	)	94	(	90	-	97	)	90	(	81	-	94	)
Fully Vaccinated (28-41 days post dose-2)	1211	24	(	2	)	91	(	87	-	94	)	89	(	83	-	93	)
Fully Vaccinated (42-55 days post dose-2)	1147	13	(	1	)	95	(	91	-	97	)	93	(	87	-	97	)
Fully Vaccinated (≥56 days post dose-2)	1029	19	(	2	)	91	(	87	-	95	)	91	(	85	-	94	)
Fully Vaccinated (56-69 days post dose-2)	864	7	(	1	)	96	(	93	-	98	)	96	(	92	-	98	)
Fully Vaccinated (70-83 days post dose-2)	665	15	(	2	)	89	(	83	-	94	)	86	(	75	-	92	)
Fully Vaccinated (84-97 days post dose-2)	411	5	(	1	)	94	(	88	-	98	)	93	(	82	-	97	)
Fully Vaccinated (≥112 days post dose-2)	206	2	(	1	)	96	(	86	-	99	)	95	(	79	-	99	)
Ad26.COV2.S (Johnson & Johnson)																	
Unvaccinated (Referent)	10761	2006	(| 19 |)												
Indeterminate Vaccination (0-13 days post dose)	78	2	(	3	)	37	(	-1	-	64	)	19	(	-41	-	53	)
Fully Vaccinated (14-27 days post dose)	135	3	(	3	)	77	(	58	-	89	)	72	(	38	-	88	)
Fully Vaccinated (28-41 days post dose)	120	6	(	5	)	76	(	55	-	89	)	69	(	34	-	86	)
Fully Vaccinated (42-55 days post dose)	132	5	(	4	)	79	(	57	-	92	)	68	(	18	-	87	)
Fully Vaccinated (≥56 days post dose)	188	6	(	3	)	85	(	72	-	93	)	79	(	48	-	91	)

[1]Adjusted model using inverse propensity weights, calculated using strata specific data, in regression doubly accounting for calendar time, daily virus circulation, age, and geographic cluster.

Table S19. Full listing of all estimates of messenger RNA (mRNA) vaccine effectiveness (VE) among COVID-19-associated emergency department and urgent care (ED/UC) medical events

					VE before Adjusted Model					VE[1]				
	Total	SARS-CoV-2 Positive	(	Row %	)	%	(	95% CI	)	%	(	95% CI	)	
mRNA VE among COVID-19 ED/UC medical events														
VE both mRNA vaccines (aged ≥50 years)														
Unvaccinated (Referent)	11812	2847	(	24.1	)									
Partially 1-Dose Vaccinated	1920	155	(	8.1	)	72	(	67 - 77	)	68	(	61 - 74	)	
Partially 2-Dose Vaccinated	1269	66	(	5.2	)	83	(	78 - 87	)	80	(	73 - 85	)	
Fully Vaccinated	6065	154	(	2.5	)	92	(	90 - 93	)	91	(	89 - 93	)	
By vaccine product among COVID-19 medical events														
VE of BioNTech-Pfizer mRNA (aged ≥50 years)														
Unvaccinated (Referent)	11812	2847	(	24.1	)									
Partially 1-Dose Vaccinated	912	88	(	9.6	)	66	(	58 - 73	)	58	(	46 - 68	)	
Partially 2-Dose Vaccinated	711	31	(	4.4	)	86	(	79 - 90	)	82	(	74 - 88	)	
Fully Vaccinated	3589	105	(	2.9	)	91	(	88 - 92	)	89	(	85 - 91	)	
VE of Moderna mRNA (aged ≥50 years)														
Unvaccinated (Referent)	11812	2847	(	24.1	)									
Partially 1-Dose Vaccinated	1008	67	(	6.6	)	78	(	71 - 83	)	73	(	64 - 79	)	
Partially 2-Dose Vaccinated	558	35	(	6.3	)	79	(	70 - 85	)	72	(	59 - 81	)	
Fully Vaccinated	2476	49	(	2.0	)	94	(	92 - 95	)	92	(	89 - 94	)	
Ad26.COV2.S (Johnson & Johnson)														
Unvaccinated (Referent)	8461	2200	(	26.0	)									
Full 1-dose Vaccinated	456	29	(	6.4	)	81	(	72 - 87	)	73	(	59 - 82	)	
By Age Group among COVID-19 medical events														
VE both mRNA vaccines (aged 50-64 years)														
Unvaccinated (Referent)	4908	1416	(	28.9	)									
Partially 1-Dose Vaccinated	547	50	(	9.1	)	75	(	67 - 82	)	73	(	63 - 80	)	
Partially 2-Dose Vaccinated	325	13	(	4.0	)	90	(	82 - 94	)	90	(	82 - 94	)	
Fully Vaccinated	1336	35	(	2.6	)	93	(	91 - 95	)	93	(	90 - 95	)	
VE both mRNA vaccines (aged 65-74 years)														

Unvaccinated (Referent)	3518	829	(	23.6	)										
Partially 1-Dose Vaccinated	611	47	(	7.7	)	73	(	63	-	80	)	72	(	61	-	80	)
Partially 2-Dose Vaccinated	403	22	(	5.5	)	81	(	71	-	88	)	81	(	69	-	88	)
Fully Vaccinated	1915	48	(	2.5	)	92	(	89	-	94	)	92	(	89	-	94	)
VE both mRNA vaccines (aged 75-84 years)																	
Unvaccinated (Referent)	2359	459	(| 19.5 |)												
Partially 1-Dose Vaccinated	539	45	(	8.3	)	62	(	48	-	73	)	59	(	41	-	71	)
Partially 2-Dose Vaccinated	369	21	(	5.7	)	75	(	61	-	84	)	63	(	39	-	78	)
Fully Vaccinated	1893	51	(	2.7	)	89	(	85	-	91	)	89	(	85	-	92	)
VE both mRNA vaccines (aged ≥85 years)																	
Unvaccinated (Referent)	1027	143	(| 13.9 |)												
Partially 1-Dose Vaccinated	223	13	(	5.8	)	62	(	31	-	79	)	44	(	-8	-	71	)
Partially 2-Dose Vaccinated	172	10	(	5.8	)	62	(	26	-	80	)	54	(	6	-	77	)
Fully Vaccinated	921	20	(	2.2	)	86	(	78	-	91	)	84	(	73	-	91	)
By Race and Ethnicity among COVID-19 medical events																	
-																	
VE both mRNA vaccines among White adults aged ≥50 years																	
Unvaccinated (Referent)	9334	2158	(| 23.1 |)												
Partially 1-Dose Vaccinated	1599	114	(	7.1	)	74	(	69	-	79	)	70	(	63	-	76	)
Partially 2-Dose Vaccinated	1076	53	(	4.9	)	83	(	77	-	87	)	78	(	70	-	84	)
Fully Vaccinated	5182	128	(	2.5	)	92	(	90	-	93	)	91	(	89	-	93	)
VE both mRNA vaccines among Black adults aged ≥50 years																	
Unvaccinated (Referent)	604	166	(| 27.5 |)												
Partially 1-Dose Vaccinated	55	7	(	12.7	)	62	(	13	-	83	)	59	(	0	-	83	)
Partially 2-Dose Vaccinated	25	1	(	4.0	)	89	(	18	-	99	)	82	(	-71	-	98	)
Fully Vaccinated	134	3	(	2.2	)	94	(	81	-	98	)	95	(	84	-	98	)
VE both mRNA vaccines among Other or Unknown aged ≥50 years																	
Unvaccinated (Referent)	1874	523	(| 27.9 |)												
Partially 1-Dose Vaccinated	266	34	(	12.8	)	62	(	45	-	74	)	57	(	37	-	71	)
Partially 2-Dose Vaccinated	168	12	(	7.1	)	80	(	64	-	89	)	84	(	70	-	92	)
Fully Vaccinated	749	23	(	3.1	)	92	(	87	-	95	)	87	(	79	-	93	)

VE both mRNA vaccines among Hispanic adults aged ≥50 years																
Unvaccinated (Referent)	725	248	(	34.2	)											
Partially 1-Dose Vaccinated	102	14	(	13.7	)	69	(	45	-	83	)	55	(	14	-	76	)
Partially 2-Dose Vaccinated	65	5	(	7.7	)	84	(	60	-	94	)	86	(	64	-	95	)
Fully Vaccinated	250	23	(	9.2	)	81	(	69	-	88	)	81	(	70	-	88	)
VE both mRNA vaccines among Non-Hispanic adults aged ≥50 years																
Unvaccinated (Referent)	11087	2599	(	23.4	)											
Partially 1-Dose Vaccinated	1818	141	(	7.8	)	73	(	67	-	77	)	68	(	61	-	74	)
Partially 2-Dose Vaccinated	1204	61	(	5.1	)	83	(	77	-	87	)	79	(	72	-	85	)
Fully Vaccinated	5815	131	(	2.2	)	92	(	91	-	94	)	92	(	90	-	93	)
<u>By Presence of Absence of Underlying Chronic Medical Conditions Associated with Increased Risk of Severe Respiratory Disease</u>																
VE both mRNA vaccines among aged ≥50 years with no chronic condition																
Unvaccinated (Referent)	4524	1446	(	32.0	)											
Partially 1-Dose Vaccinated	634	82	(	12.9	)	68	(	60	-	75	)	64	(	53	-	73	)
Partially 2-Dose Vaccinated	393	30	(	7.6	)	82	(	74	-	88	)	81	(	71	-	87	)
Fully Vaccinated	1805	52	(	2.9	)	94	(	92	-	95	)	93	(	90	-	95	)
VE both mRNA vaccines among aged ≥50 years with ≥1 chronic respiratory condition																
Unvaccinated (Referent)	3832	677	(	17.7	)											
Partially 1-Dose Vaccinated	703	36	(	5.1	)	75	(	64	-	82	)	67	(	53	-	77	)
Partially 2-Dose Vaccinated	463	20	(	4.3	)	79	(	67	-	87	)	77	(	62	-	86	)
Fully Vaccinated	2206	44	(	2.0	)	91	(	87	-	93	)	90	(	86	-	93	)
VE both mRNA vaccines among aged ≥50 years with ≥1 chronic non-respiratory condition																
Unvaccinated (Referent)	6483	1293	(	19.9	)											
Partially 1-Dose Vaccinated	1179	67	(	5.7	)	76	(	69	-	81	)	72	(	63	-	79	)
Partially 2-Dose Vaccinated	796	33	(	4.2	)	83	(	75	-	88	)	78	(	68	-	85	)
Fully Vaccinated	3947	98	(	2.5	)	90	(	87	-	92	)	90	(	87	-	92	)
<u>By Alternative Clinical Outcomes</u>																

VE both mRNA vaccines among aged ≥50 years with acute respiratory illness diagnosis															
Unvaccinated (Referent)	6785	2541	(	37.5	)										
Partially 1-Dose Vaccinated	992	136	(	13.7	)	73	(	68	-	78	)	68	(	61	-	74	)
Partially 2-Dose Vaccinated	606	54	(	8.9	)	84	(	78	-	88	)	82	(	76	-	87	)
Fully Vaccinated	2992	135	(	4.5	)	92	(	91	-	93	)	92	(	90	-	93	)
VE both mRNA vaccines among aged ≥50 years with clinical pneumonia diagnosis															
Unvaccinated (Referent)	1962	930	(	47.4	)										
Partially 1-Dose Vaccinated	220	36	(	16.4	)	78	(	69	-	85	)	76	(	64	-	84	)
Partially 2-Dose Vaccinated	165	14	(	8.5	)	90	(	82	-	94	)	87	(	76	-	93	)
Fully Vaccinated	797	33	(	4.1	)	95	(	93	-	97	)	95	(	93	-	97	)
VE both mRNA vaccines among aged ≥50 years with CLI/**signs and symptoms** as primary discharge code															
Unvaccinated (Referent)	6885	2365	(	34.4	)										
Partially 1-Dose Vaccinated	944	122	(	12.9	)	72	(	65	-	77	)	68	(	60	-	74	)
Partially 2-Dose Vaccinated	599	46	(	7.7	)	84	(	78	-	88	)	83	(	76	-	88	)
Fully Vaccinated	2619	109	(	4.2	)	92	(	90	-	93	)	91	(	89	-	93	)

[1]Adjusted model using inverse propensity weights, calculated using strata specific data, in regression doubly accounting for calendar time, daily virus circulation, age, and geographic cluster.

Table_S20. Full listing of all estimates of messenger RNA (mRNA) vaccine effectiveness (VE) among COVID-19-associated emergency department and urgent care (ED/UC) medical events by days past most recent dose

				VE before Adjusted Model		VE[1]	
	Total	SARS-CoV-2 Positive	Row %	%	95% CI	%	95% CI
mRNA VE against COVID-19 ED/UC							
VE COVID-19 vaccines (aged ≥50 years)							
Unvaccinated (Referent)	11812	2847	24.1				
Indeterminate Vaccination (0-13 days post dose-1)	1255	252	20.1	21	9 - 32	6	-10 - 20
Partially 1-Dose Vaccinated (14-27 days post dose-1)	1346	128	9.5	67	60 - 73	63	54 - 69
Partially 1-Dose Vaccinated (28-41 days post dose-1)	307	18	5.9	80	68 - 88	77	59 - 87
Partially 1-Dose Vaccinated (42-55 days post dose-1)	72	2	2.8	91	63 - 98	91	60 - 98
Partially 1-Dose Vaccinated (≥56 days post dose-1)	195	7	3.6	88	75 - 94	88	73 - 95
Partially 2-Dose Vaccinated (0-13 days post dose-2)	1269	66	5.2	83	78 - 87	80	74 - 85
Fully Vaccinated (14-27 days post dose-2)	1198	23	1.9	94	91 - 96	92	88 - 95
Fully Vaccinated (28-41 days post dose-2)	1170	20	1.7	95	91 - 96	95	92 - 97
Fully Vaccinated (42-55 days post dose-2)	1067	18	1.7	95	91 - 97	95	91 - 97
Fully Vaccinated (56-69 days post dose-2)	924	28	3.0	90	86 - 93	88	81 - 92
Fully Vaccinated (70-83 days post dose-2)	667	24	3.6	88	82 - 92	86	78 - 91
Fully Vaccinated (84-97 days post dose-2)	487	13	2.7	91	85 - 95	92	87 - 96
Fully Vaccinated (98-111 days post dose-2)	331	17	5.1	83	72 - 90	86	77 - 92
Fully Vaccinated (≥112 days post dose-2)	221	11	5.0	84	70 - 91	86	74 - 93
By mRNA vaccine product against COVID-19 ED/UC							
VE of BioNTech-Pfizer mRNA (aged ≥50 years)							
Unvaccinated (Referent)	11812	2847	24.1				
Indeterminate Vaccination (0-13 days post dose-1)	673	129	19.2	25	9 - 39	1	-25 - 22
Partially 1-Dose Vaccinated (14-27 days post dose-1)	685	76	11.1	61	50 - 69	53	38 - 65
Partially 1-Dose Vaccinated (28-41 days post dose-1)	97	8	8.2	72	42 - 86	77	47 - 90
Partially 1-Dose Vaccinated (42-55 days post dose-1)	33	0	0.0	NC[2]	NC[2] - NC[2]	NC[2]	NC[2] - NC[2]
Partially 1-Dose Vaccinated (≥56 days post dose-1)	97	4	4.1	86	63 - 95	80	39 - 94
Partially 2-Dose Vaccinated (0-13 days post dose-2)	711	31	4.4	86	79 - 90	83	74 - 88
Fully Vaccinated (14-27 days post dose-2)	725	13	1.8	94	90 - 97	93	87 - 96
Fully Vaccinated (28-41 days post dose-2)	680	13	1.9	94	89 - 96	94	90 - 97
Fully Vaccinated (42-55 days post dose-2)	608	8	1.3	96	92 - 98	93	81 - 97
Fully Vaccinated (56-69 days post dose-2)	548	18	3.3	89	83 - 93	82	68 - 90
Fully Vaccinated (70-83 days post dose-2)	391	18	4.6	85	76 - 91	80	66 - 88

Fully Vaccinated (84-97 days post dose-2)	275	9	(	3.3	)	89	(	79	-	95	)	91	(	82	-	96	)
Fully Vaccinated (98-111 days post dose-2)	224	17	(	7.6	)	74	(	58	-	84	)	78	(	61	-	87	)
Fully Vaccinated (≥112 days post dose-2)	138	9	(	6.5	)	78	(	57	-	89	)	83	(	64	-	92	)
VE of Moderna mRNA (aged ≥50 years)																	
Unvaccinated (Referent)	11812	2847	(	24.1	)												
Indeterminate Vaccination (0-13 days post dose-1)	582	123	(	21.1	)	16	(	-3	-	31	)	0	(	-25	-	21	)
Partially 1-Dose Vaccinated (14-27 days post dose-1)	661	52	(	7.9	)	73	(	64	-	80	)	67	(	56	-	76	)
Partially 1-Dose Vaccinated (28-41 days post dose-1)	210	10	(	4.8	)	84	(	70	-	92	)	78	(	54	-	90	)
Partially 1-Dose Vaccinated (42-55 days post dose-1)	39	2	(	5.1	)	83	(	30	-	96	)	87	(	41	-	97	)
Partially 1-Dose Vaccinated (≥56 days post dose-1)	98	3	(	3.1	)	90	(	69	-	97	)	92	(	72	-	97	)
Partially 2-Dose Vaccinated (0-13 days post dose-2)	558	35	(	6.3	)	79	(	70	-	85	)	74	(	62	-	82	)
Fully Vaccinated (14-27 days post dose-2)	473	10	(	2.1	)	93	(	87	-	96	)	90	(	81	-	95	)
Fully Vaccinated (28-41 days post dose-2)	490	7	(	1.4	)	95	(	90	-	98	)	96	(	92	-	98	)
Fully Vaccinated (42-55 days post dose-2)	459	10	(	2.2	)	93	(	87	-	96	)	93	(	85	-	96	)
Fully Vaccinated (≥56 days post dose-2)	376	10	(	2.7	)	91	(	84	-	95	)	90	(	79	-	95	)
Fully Vaccinated (56-69 days post dose-2)	276	6	(	2.2	)	93	(	84	-	97	)	91	(	79	-	96	)
Fully Vaccinated (70-83 days post dose-2)	212	4	(	1.9	)	94	(	84	-	98	)	91	(	74	-	97	)
Fully Vaccinated (84-97 days post dose-2)	107	0	(	0.0	)	NC[2]	(	NC[2]	-	NC[2]	)	NC[2]	(	NC[2]	-	NC[2]	)
Fully Vaccinated (≥112 days post dose-2)	83	2	(	2.4	)	92	(	68	-	98	)	90	(	52	-	98	)
Ad26.COV2.S (Johnson & Johnson)																	
Unvaccinated (Referent)	8461	2200	(	26.0	)												
Indeterminate Vaccination (0-13 days post dose)	81	15	(	18.5	)	35	(	-14	-	63	)	25	(	-37	-	59	)
Fully Vaccinated (14-27 days post dose)	119	8	(	6.7	)	79	(	58	-	90	)	67	(	30	-	84	)
Fully Vaccinated (28-41 days post dose)	99	6	(	6.1	)	82	(	58	-	92	)	80	(	52	-	92	)
Fully Vaccinated (42-55 days post dose)	81	7	(	8.6	)	73	(	41	-	88	)	58	(	5	-	81	)
Fully Vaccinated (≥56 days post dose)	157	8	(	5.1	)	85	(	69	-	93	)	87	(	71	-	94	)

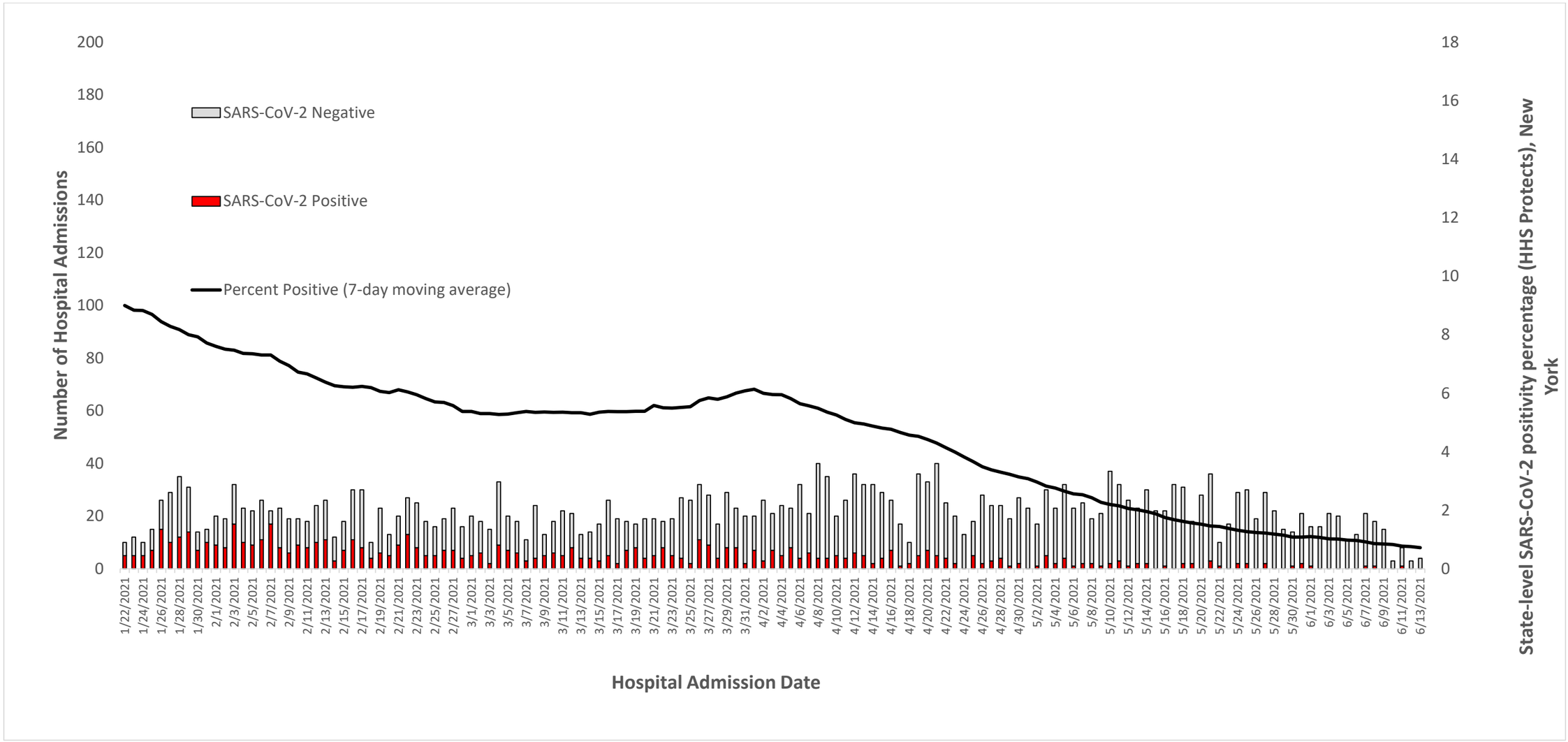
[1]Adjusted model using inverse propensity weights, calculated using strata specific data, in regression doubly accounting for calendar time, daily virus circulation, age, and geographic cluster.

[2]Not Calculated due to no breakthrough cases.

Section S2. Supplemental Figures Referenced in the Main Manuscript

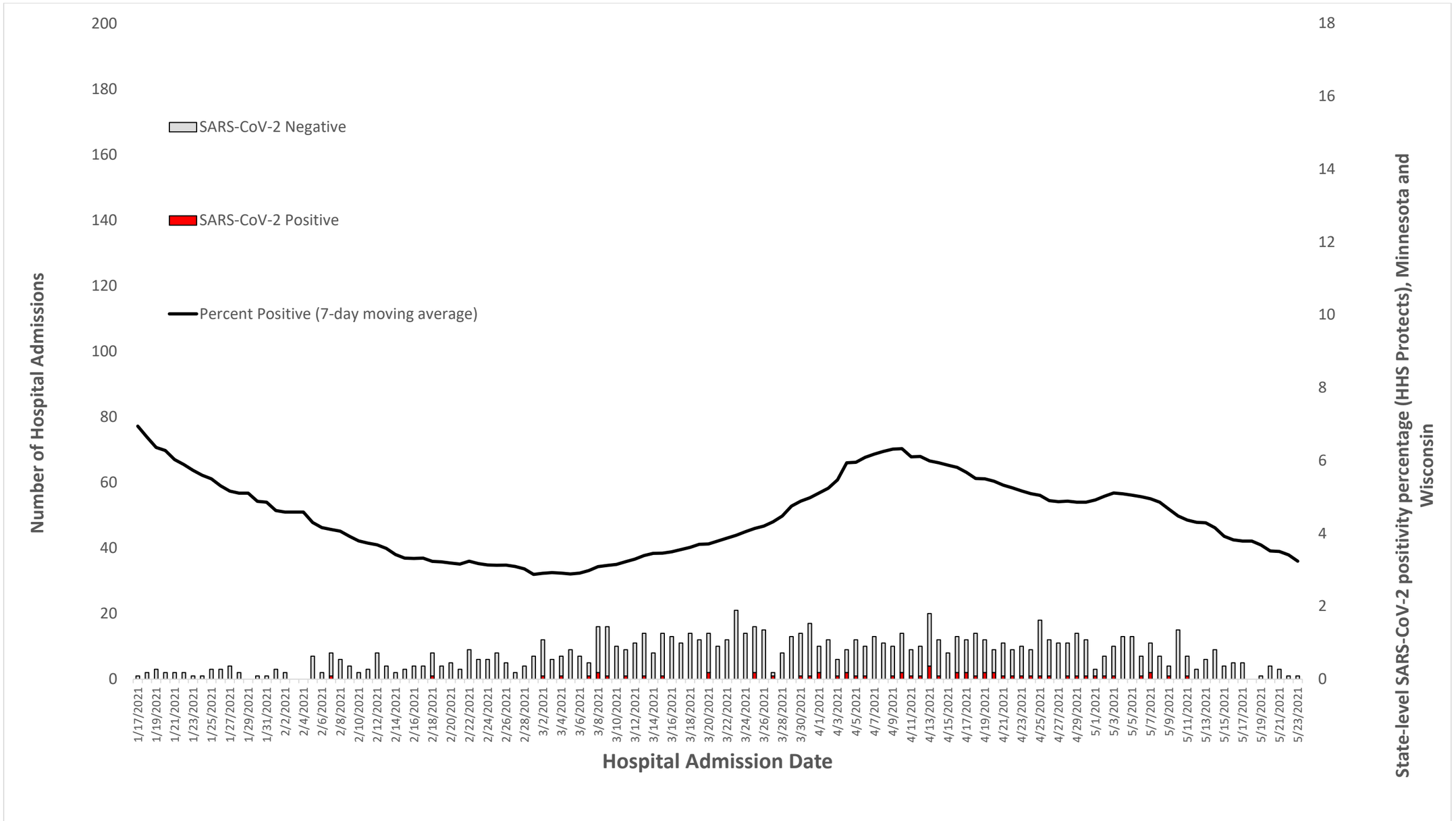
Figures_S1-S10: Epi-curves with local percent positivity by Partner Sites

Figure S1: Hospital admission for all adults with a COVID-like illness in analytic sample from COLUMBIA UNIVERSITY, with local percent positivity by date



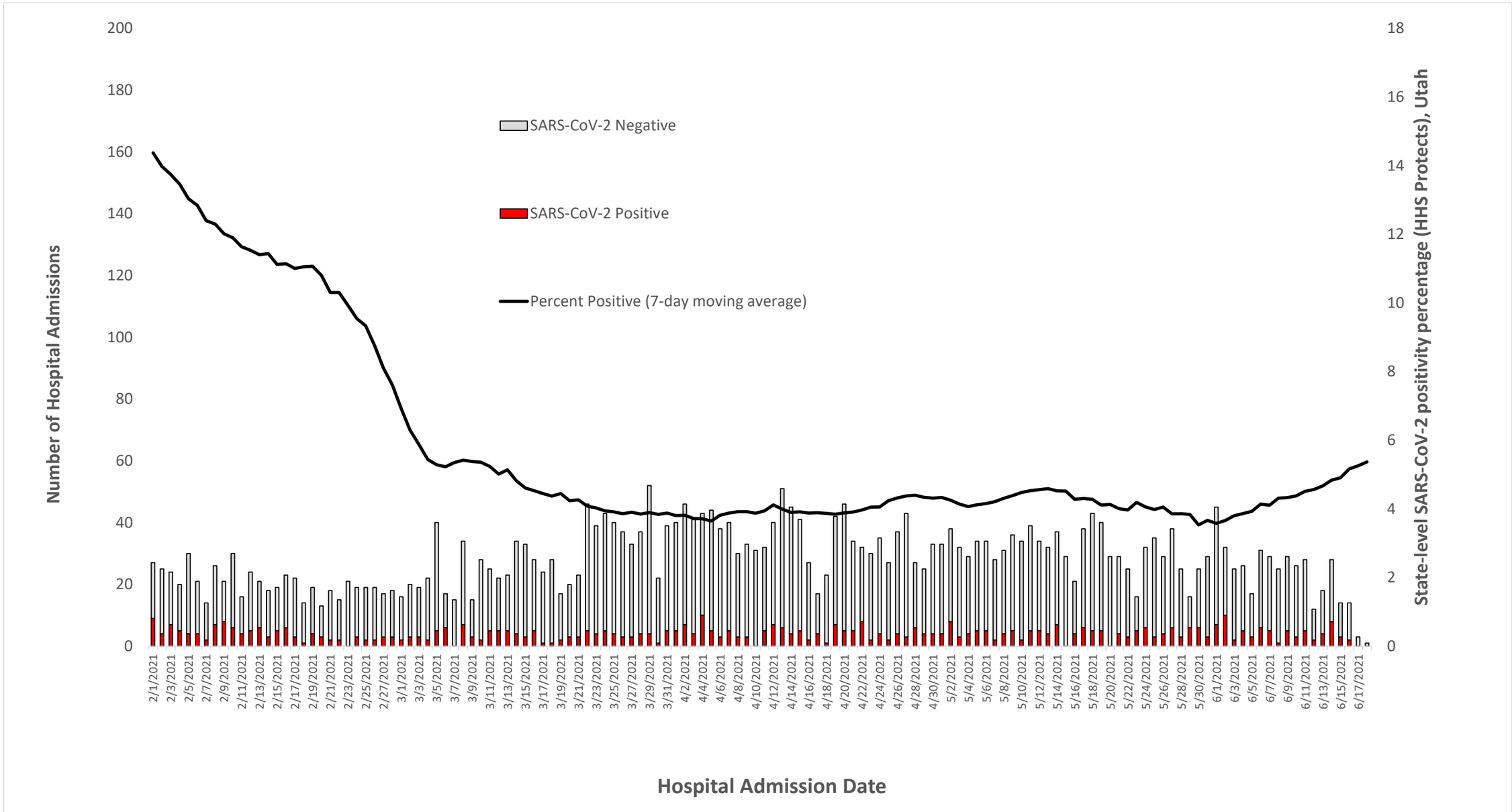
Footnote: For Columbia University Irving Medical Center, hospitalizations starting on January 22 were included in the analytic sample, reflecting hospitalizations among patients in at least one age group that occurred 14 days after the date of local vaccine availability.

Figure S2: Hospital admission for all adults with a COVID-like illness in analytic sample from HEALTHPARTNERS, with local percent positivity by date



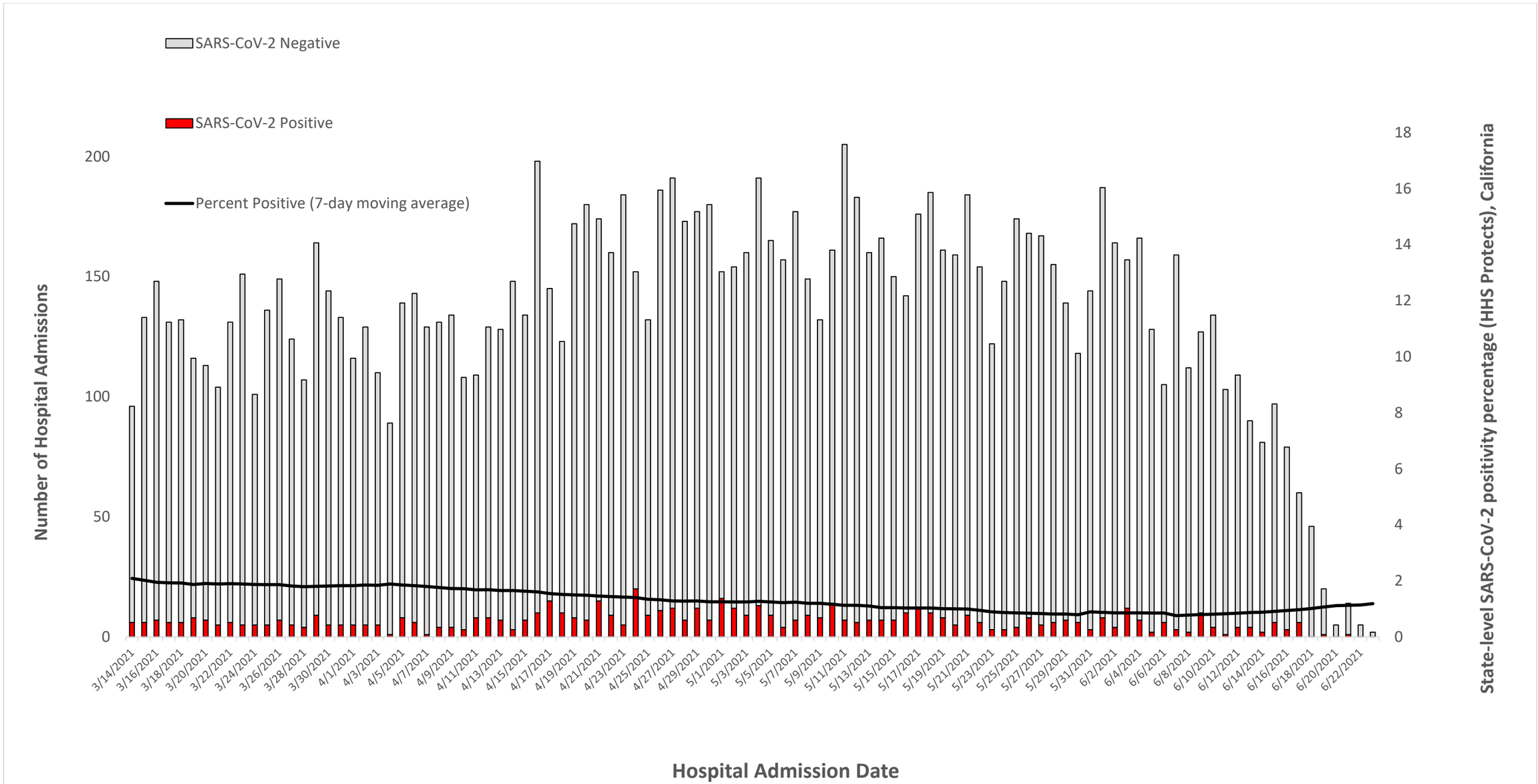
Footnote: For HealthPartners, hospitalizations starting on January 17 were included in the analytic sample, reflecting hospitalizations among patients in at least one age group that occurred 14 days after the date of local vaccine availability.

Figure S3: Hospital admission for all adults with a COVID-like illness in analytic sample from INTERMOUNTAIN HEALTHCARE, with local percent positivity by date



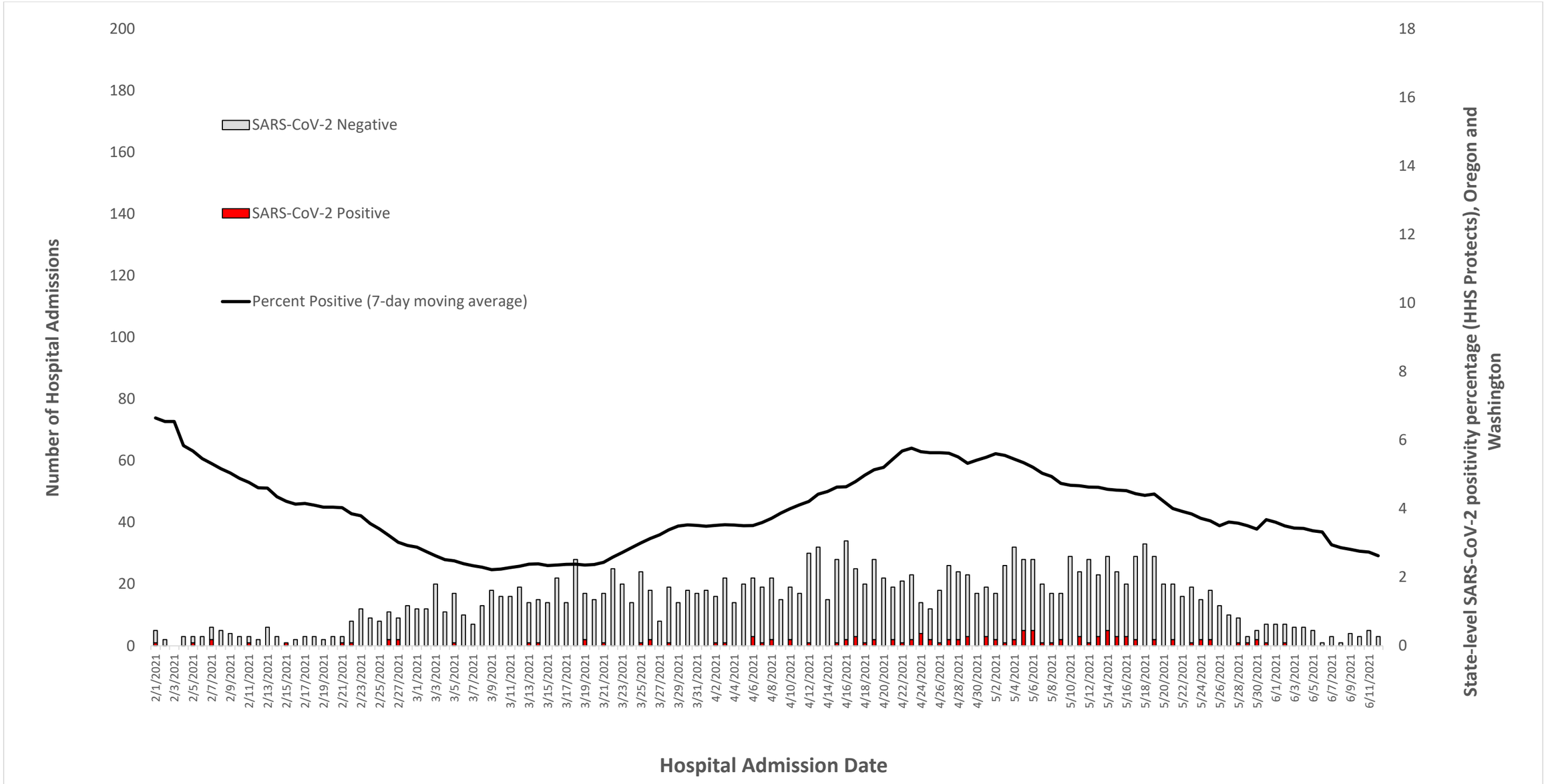
Footnote: For Intermountain Healthcare, hospitalizations starting on February 1 were included in the analytic sample, reflecting hospitalizations among patients in at least one age group that occurred 14 days after the date of local vaccine availability.

Figure S4: Hospital admission for all adults with a COVID-like illness in analytic sample from KAISER PERMANENTE NORTHERN CALIFORNIA, with local percent positivity by date



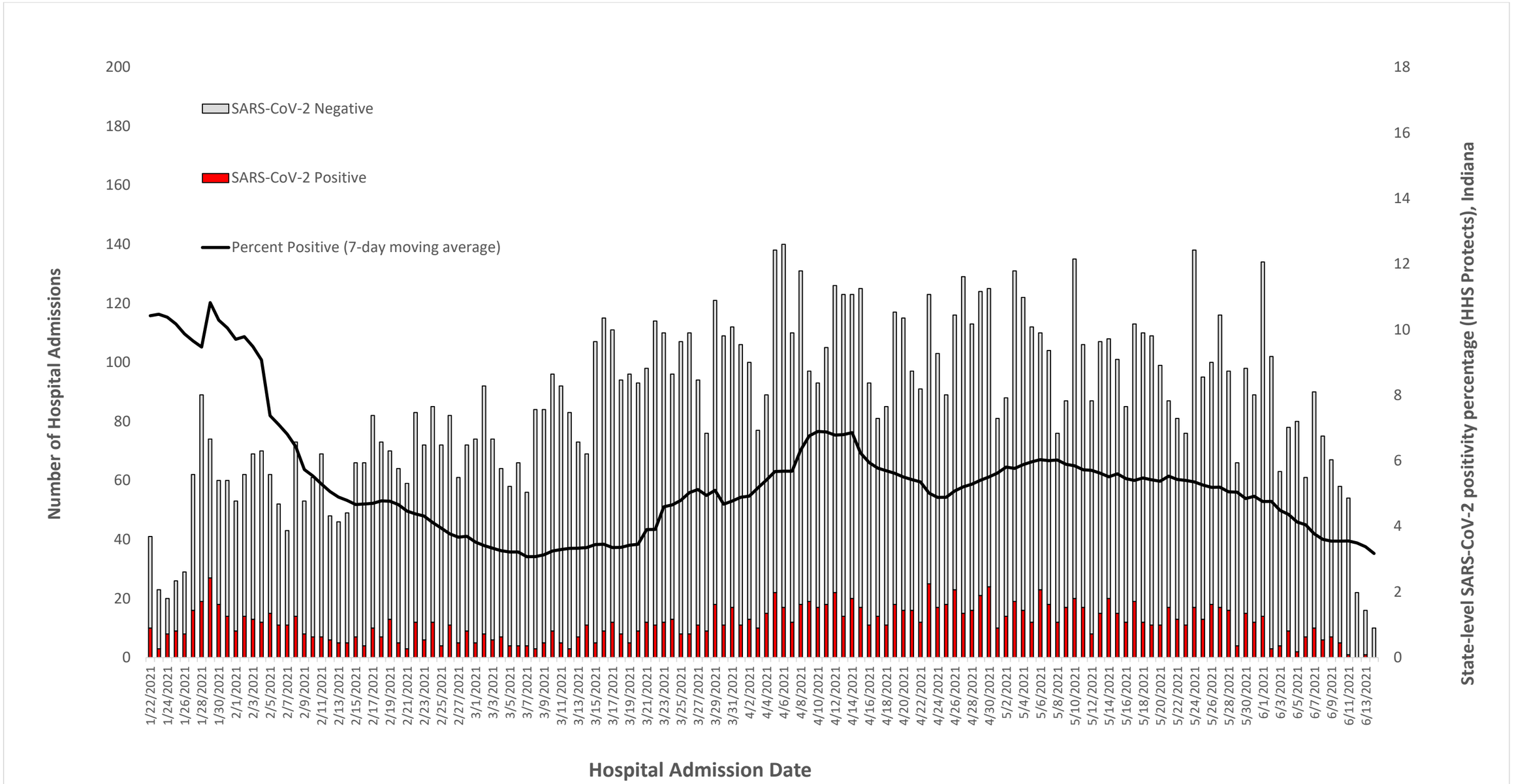
Footnote: For Kaiser Permanente Northern California, hospitalizations starting on March 14 were included in the analytic sample, reflecting hospitalizations among patients in at least one age group that occurred 14 days after the date of local vaccine availability.

Figure S5: Hospital admission for all adults with a COVID-like illness in analytic sample from KAISER PERMANENTE NORTHWEST, with local percent positivity by date



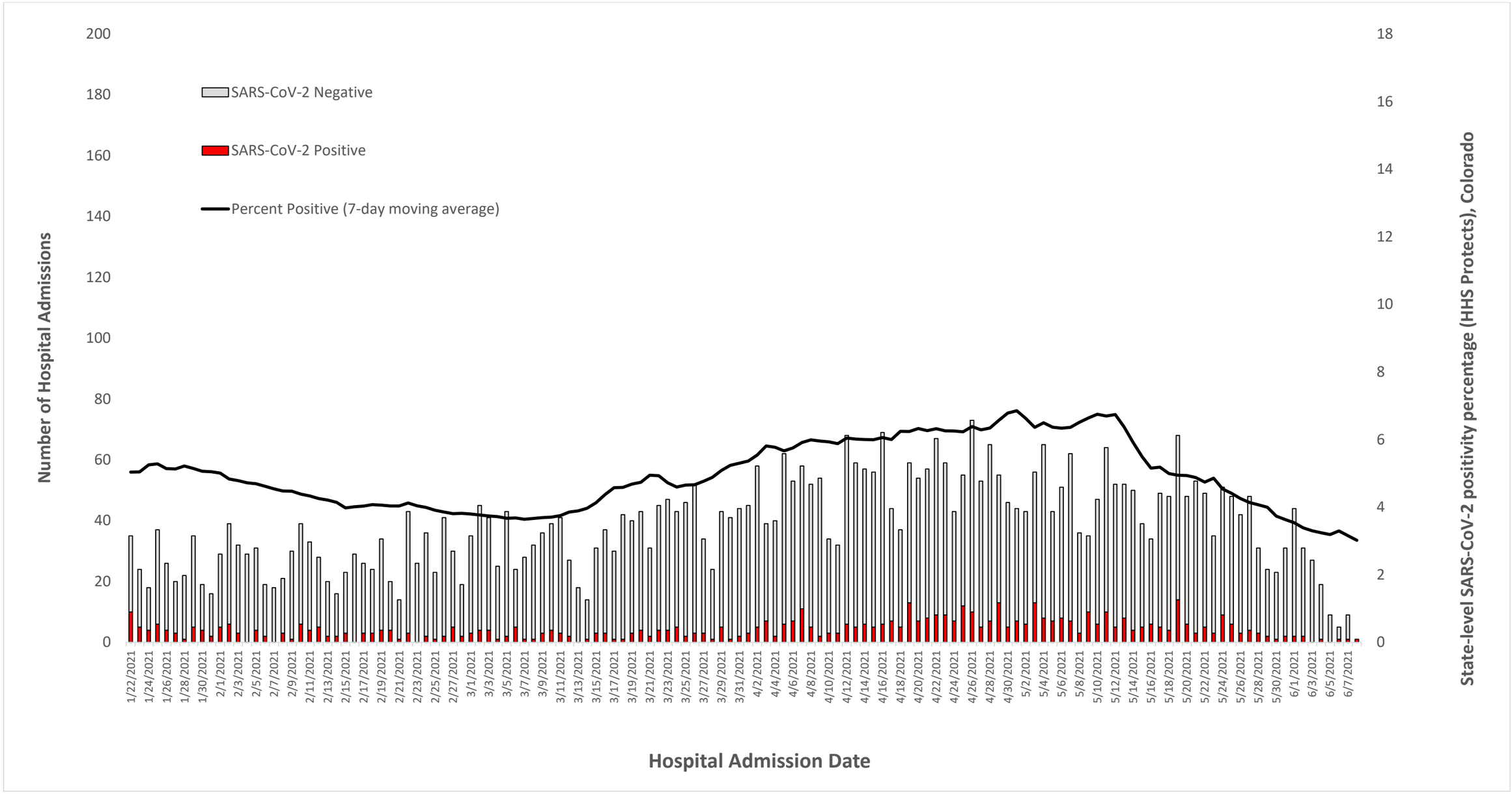
Footnote: For Kaiser Permanente Northwest, hospitalizations starting on February 1 were included in the analytic sample, reflecting hospitalizations among patients in at least one age group that occurred 14 days after the date of local vaccine availability.

Figure S6: Hospital admission for all adults with a COVID-like illness in analytic sample from REGENSTRIEF INSTITUTE, with local percent positivity by date



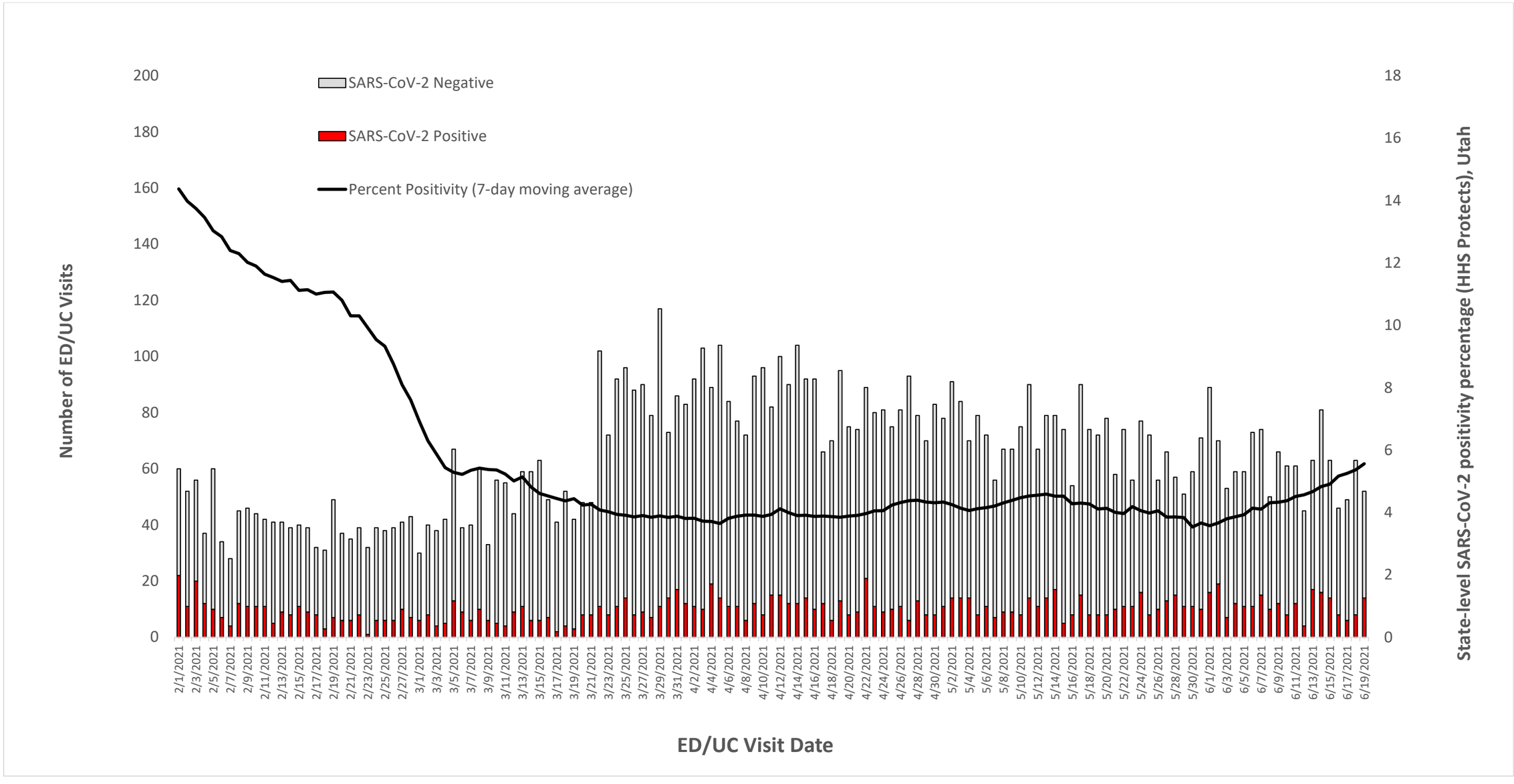
Footnote: For Regenstrief Institute, hospitalizations starting on January 22 were included in the analytic sample, reflecting hospitalizations among patients in at least one age group that occurred 14 days after the date of local vaccine availability.

Figure S7: Hospital admission for all adults with a COVID-like illness in analytic sample from UNIVERSITY OF COLORADO, with local percent positivity by date



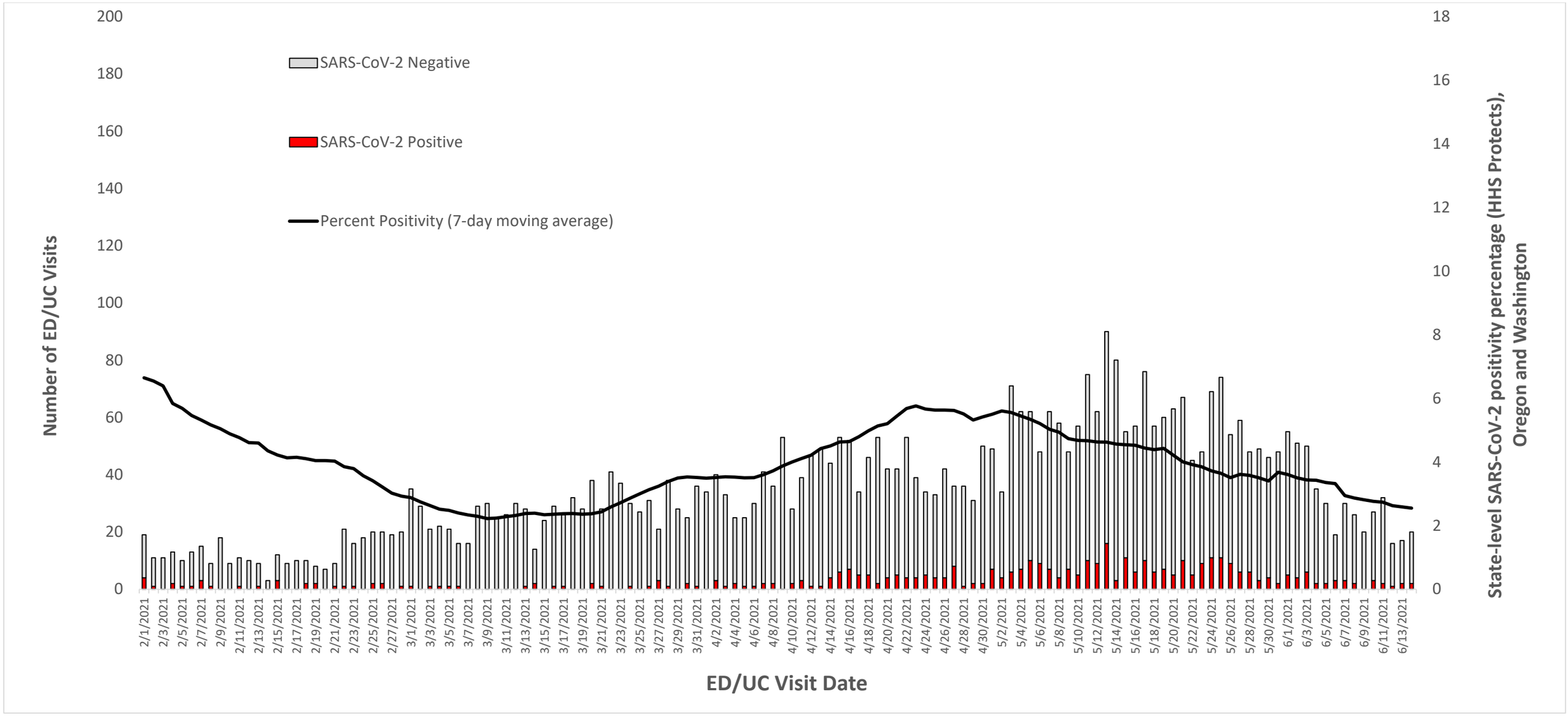
Footnote: For University of Colorado, ED/UC encounters starting on January 22 were included in the analytic sample, reflecting encounters among patients in at least one age group that occurred 14 days after the date of local vaccine availability.

Figure S8: Emergency department and urgent care (ED/UC) visits for all adults with a COVID-like illness in analytic sample from INTERMOUNTAIN HEALTHCARE, with local percent positivity by date



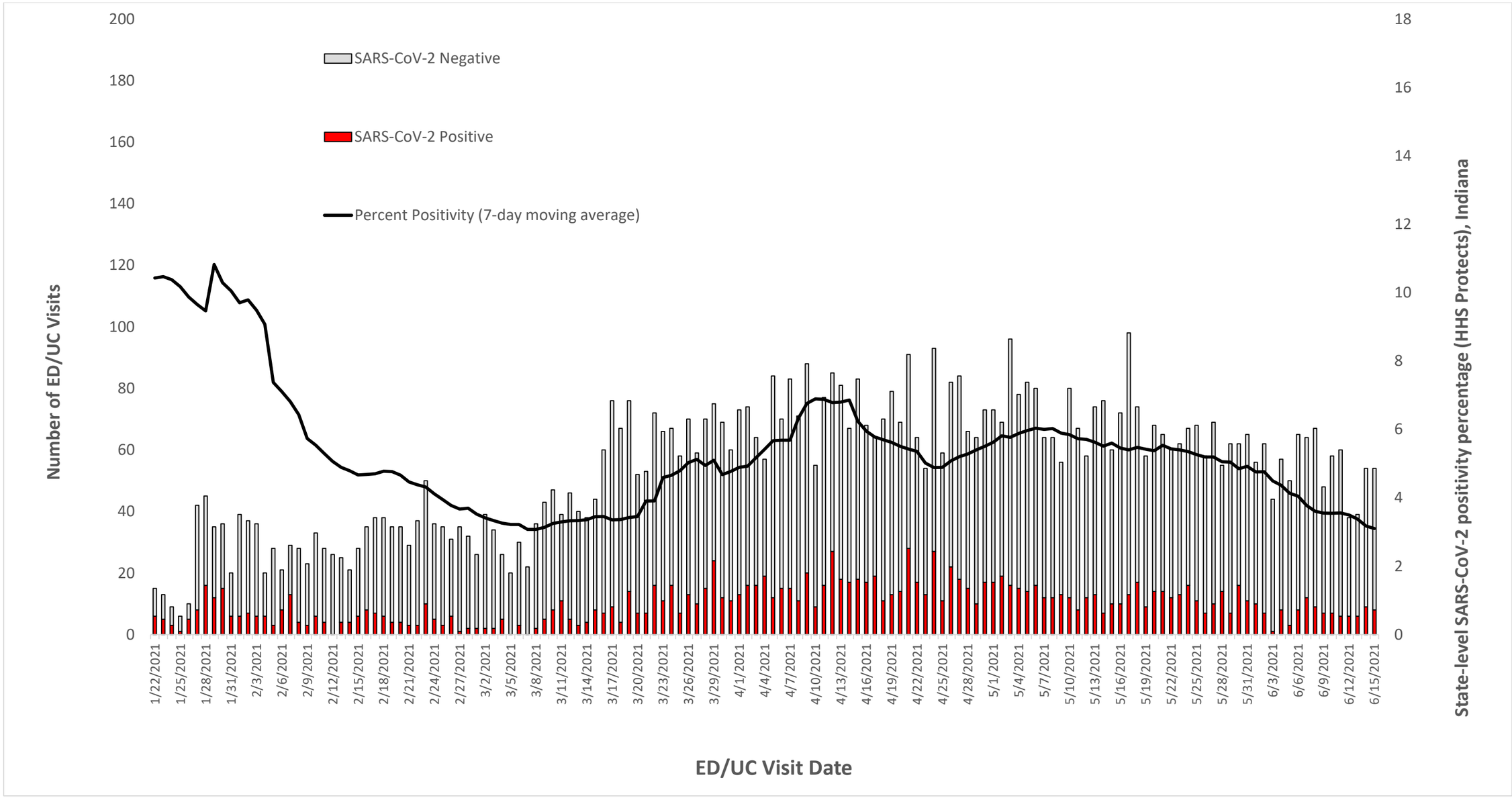
Footnote: For Intermountain Healthcare, ED/UC encounters starting on February 1 were included in the analytic sample, reflecting encounters among patients in at least one age group that occurred 14 days after the date of local vaccine availability.

Figure S9: Emergency department and urgent care (ED/UC) visits for all adults with a COVID-like illness in analytic sample from KAISER PERMANENTE NORTHWEST, with local percent positivity by date



Footnote: For Kaiser Permanente Northwest, ED/UC encounters starting on February 22 were included in the analytic sample, reflecting encounters among patients in at least one age group that occurred 14 days after the date of local vaccine availability.

Figure S10: Emergency department and urgent care (ED/UC) visits for all adults with a COVID-like illness in analytic sample from REGENSTRIEF INSTITUTE, with local percent positivity by date



Footnote: For Regenstrief Institute, ED/UC encounters starting on January 22 were included in the analytic sample, reflecting encounters among patients in at least one age group that occurred 14 days after the date of local vaccine availability

Section S3. Supplemental Methods

A. Study Design:

1. Inclusion/Exclusion criteria

Medical encounters that occurred since January 1, 2021 were initially identified, and exclusions were then applied to ultimately obtain the analytic population of interest. The inclusion criteria were medical encounters among adults (aged ≥50 years) with a qualified COVID-like illness (CLI) diagnosis, a positive or negative result from a molecular SARS-CoV-2 laboratory test within the 14 days before and up to 72-hours after the hospital admission or Emergency Department or Urgent Care (ED/UC) encounter, and an opportunity to be at least partially vaccinated on the index date (defined as 14 days after the partner-specific date of when vaccines became widely available to adults in each age group). Hospitalizations were excluded if they lasted <24 hours. Medical events were excluded if they occurred prior to age-specific inclusion dates within a partner's catchment area or if the days from discharge were less than the lag time for vaccine record update. Data from hospital readmissions within 30 days of a previous hospital discharge, repeat ED encounters within 24 hours, and repeat UC encounters within 24 hours were combined and analyzed as single medical encounters. ED/UC encounters that resulted in hospitalization were considered as separate medical encounters because data for encounters across multiple settings were not consistently linked together and in order to also capture ED/UC encounters regardless of whether they resulted in hospitalization. Medical events were also excluded if no molecular SARS-CoV-2 testing was performed within 14 days to 72-hours after admission or if they occurred in patients who received a first dose of a COVID-19 vaccine <14 days prior to the index medical event date.

2. Outcome definition

The outcome of interest is laboratory-confirmed SARS-CoV-2 CLI-associated medical event, which is based on clinical testing and clinical diagnosis.

Qualified clinical tests for SARS-CoV-2 were real-time reverse transcription polymerase chain reaction (RT-PCR) and molecular assays. Patients tested using only a non-molecular assay (e.g., rapid SARS-CoV-2 antigen test) were excluded. We defined a clinical testing window to capture tests that occurred within 14 days before and up to 72-hours after the hospital admission or ED/UC encounter date. The following hierarchy was used if multiple tests occurred in the 17-day window. Positive results took precedence over negative test results. If multiple concordant test results were available within the 17-day window, the result closest to the hospitalization was preferred (particularly if the test occurred before the encounter). If multiple test types were associated with a given encounter, molecular assay results (e.g., RT-PCR) were preferred over rapid molecular assays. In addition, each test could have up to three associated dates, and if more than one date was available, the following hierarchy was applied: 1) date of specimen collection, 2) date the test was performed, and 3) date of available test results. Ultimately, the index date for each medical event was defined as the date of the most recent positive or negative result from a molecular assay prior to the medical event or the date of the medical event if testing only occurred within 72-hours after the admission or encounter date.

A qualified CLI diagnosis was defined as the presence of ≥1 ICD code either at hospital discharge or associated with the ED/UC medical event for the following diagnostic categories or signs and symptoms of acute illness: COVID-19 disease, pneumonia (etiology types included

COVID-19, influenza, other viral, and bacterial/other), influenza disease, acute respiratory distress syndrome, chronic obstructive pulmonary disease exacerbation, asthma exacerbation, respiratory failure, other acute lower respiratory tract infections, acute and chronic sinusitis, acute upper respiratory tract infections, and signs and symptoms of acute febrile, respiratory, and non-respiratory illness. Table S2 lists the disease conditions defined as a qualified CLI diagnosis and corresponding ICD-9 and -10 codes.

Based on these two criteria, a COVID-19 case was defined by the presence of ≥1 positive result from a qualified test during the 17-day window and ≥1 qualified CLI diagnosis either at hospital discharge or associated with the ED/UC medical event. A control was defined as having ≥1 qualified CLI diagnosis with only negative results from a qualified test.

3. COVID-19 Vaccination Status

Vaccination status was defined as fully vaccinated, partially vaccinated, unvaccinated, and indeterminate based on timing of the vaccine receipt relative to the index testing date that categorized the event as SARS-CoV-2 positive or negative. Those with an indeterminate vaccination status were excluded from the analysis. Of note, partial vaccination was further differentiated based on receipt of the first or second dose, as described in the table below.

Vaccination status	Vaccine	Definition
Fully vaccinated	Pfizer, Moderna	Receipt of second dose in the 2-dose series occurred ≥14 days before the index testing date
	Janssen/Johnson & Johnson (J&J)	Receipt of the first dose occurred ≥14 days before the index testing date
Partially vaccinated – 1 dose	Pfizer, Moderna	No record of a second dose and receipt of first dose in the 2-dose series occurred ≥14 days before the index testing date
Partially vaccinated – 2 doses	Pfizer, Moderna	Confirmed receipt of 2 doses of vaccine, but the second dose occurred <14 days before the index testing date
Unvaccinated	Pfizer, Moderna and J&J	No record of any vaccine receipt
Indeterminate	Pfizer, Moderna and J&J	Received the first dose of any vaccine <14 days from the index test date

B. Extracting Percent Positivity Data from HHS Protect

National laboratory testing data, including data on the state and county level, are available on the password-protected HHS Protect Public Data Hub. Laboratory testing data include viral COVID-19 laboratory test [Reverse Transcription Polymerase chain reaction (RT-PCR)] results from over 1,000 U.S. laboratories and testing locations including commercial and reference laboratories, public health laboratories, hospital laboratories, and other testing locations. Data presented in HHS Protect are representative of diagnostic specimens being tested and reflects the majority of, but not all, COVID-19 testing being conducted in the United States.

For this analysis, daily laboratory data are downloaded from HHS Protect and aggregated to the state and/or county by date of report. The percent positive seven-day moving average is calculated by taking the average of the daily percent positive cases over the past seven days. The percent positive for each site-region is calculated using a weighted average based on the population of the counties within each site-region. The percent positive seven-day moving average is then plotted to show the daily trends in COVID-19 testing in specific geographic areas.

C. Analysis: VISION COVID-19 VE Statistical Analysis Plan

The primary objective of this analysis was to estimate COVID-19 vaccine effectiveness (VE) in preventing medical events associated with laboratory-confirmed SARS-CoV-2 infection, including hospitalizations and ED/UC encounters.

Overall Study Design

An EHR-based, test-negative study design was implemented where cases were defined as patients with COVID-like illness who tested positive for SARS-CoV-2 infection, and controls defined as patients with COVID-like illness who tested negative for infection. The test-negative design has been used extensively to estimate VE among medically attended influenza virus illness and is believed to minimize biases associated with access to vaccines and healthcare seeking behaviors (1,2). Vaccination against SARS-CoV-2 virus was the exposure of interest.

Vaccination Status

Full 2-dose mRNA vaccination was defined as receipt of dose 2 of either mRNA vaccine ≥14 days prior to the index date, regardless of the number of days between 2 doses. We examined two categories of partial mRNA vaccination. Partial 1-dose vaccination included patients who received their first dose ≥14 days before but who had not received dose 2 by the index date. Partial 2-dose vaccination included patients who were 1–13 days post-dose 2 (and thus not considered fully vaccinated) on the index date. Full 1-dose vaccination with the Johnson & Johnson COVID-19 vaccine (index date ≥14-days after the single dose) was examined

separately. If the index date occurred during days 1-13 following dose one of any COVID-19 vaccine, the medical encounter was excluded because immunity was considered indeterminate.

Bivariate Analyses

Bivariate analyses were conducted at the pooled and site levels. COVID-19 vaccination status by *a priori* determined covariates of interest was assessed for significant differences in characteristics of participants, with significant differences between groups defined as a standardized mean or proportion difference ≥ 0.10. Laboratory-confirmed SARS-CoV-2 infection status by covariates of interest was also assessed through bivariate analysis.

Multivariate Analyses

Analyses were conducted separately for hospitalization and ED/UC cohorts. Event data was pooled across all study partners for estimation of overall VE among hospitalization, while data was pooled across three partners (IH, RG, and KPNW) for the estimation of overall VE among ED/UC medical events. COVID-19 VE was estimated using multivariate logistic regression where VE= [1−odds ratio]x100%. The hospitalization odds ratio was defined as the ratio of the odds of hospitalization associated with SARS-CoV-2 infection among vaccinated participants to the odds of hospitalization associated with SARS-CoV-2 infection among unvaccinated participants. Similarly, the ED/UC medical event odds ratio was defined as the odds of an ED/UC medical event associated with SARS-CoV-2 infection among vaccinated participants to

the odds of an ED/UC medical event associated with SARS-CoV-2 infection among unvaccinated participants.

Since data were collected at the event- rather than person-level, the percentage of repeated measures were checked periodically. Repeated measure observations were expected to be low within the study's time frame, however, if repeated measures within a setting exceed 10%, sensitivity analyses were conducted to assess the effect of within-person correlation on VE and confidence intervals.

Initial multivariate analyses were conducted by incorporating covariates directly into the logistic regression model. Covariates for inclusion are those determined through bivariate analyses to be significantly associated with both the outcome and exposure, as well as those determined *a priori*. Preliminary estimates of VE were determined for fully and vaccinated patients. SAS version 9.4 was used for these analyses.

Multivariate analyses were conducted using an inverse propensity-score weighting method to further ensure balance among measured characteristics in the vaccinated and unvaccinated groups. Using established methods for estimating propensity scores within case-control studies (3), we first estimated propensity-for-vaccination scores among test-negative controls, then used the fitted model to calculate propensity-for-vaccination scores for test-positive observations. Vaccinated patients were weighted by the inverse of their propensity to be vaccinated. Unvaccinated patients were weighted by the inverse of their propensity to not be vaccinated. A dichotomous vaccination variable (≥14-days after first vaccine dose) was used for

propensity modeling. Propensity to vaccinate was estimated using boosted regression trees (BRT), a nonparametric sequential regression technique (4). A standardized mean or proportion difference <0.2 was the cut-off for balance. Three covariates were included directly in the regression model to account for possible residual confounding remaining after BRT modeling. These include site-regions, local-level COVID-19 percent positivity (as spline), and calendar time (as spline). Any covariates not meeting the PS cut-off for balance were also included directly in the regression model.

Regularization settings used to prevent over fitting by BRT methods were determined based on overall sample size, however, the following guidelines were followed: shallow tree depth (2-3 interaction levels), large number of trees (1000-5000), low learning rate (<=0.01), and 50-75% bagging. Propensity score weights were designed to estimate overall average treatment effect. Covariates for inclusion in the propensity model included those related to both the outcome and exposure, as well as those determined *a priori* for inclusion.

Applying best practices for using inverse probability of treatment weights described by Austin and Stuart (5), the distributions of weights were examined for each VE model and presented in supplementary tables (see Supplementary Results). Across all models, outlying weights were found at the extreme upper ends of the distributions. Therefore, we truncated weights at the 99.9 percentile for each model.

Propensities and weights were calculated using the 'twang' R package (6). All propensity-score analyses were conducted using R version 4.0.3.

Covariates

Covariates that were expected or found to be associated with the likelihood of COVID-19 vaccination and the likelihood of COVID-19 positivity were included in the model.

To account for changes over time in vaccination uptake and virus circulation, calendar time in days was included in the BRT algorithms as a continuous covariate and in the regression model as a spline term. As a proxy for risk of infection, local-level percent-positive COVID-like illness times local-level percent-positive SARS-CoV-2 infection was included in both BRT and regression models. Spline functions for both calendar time and percent-positivity were defined as natural cubic splines with knots at quartiles. To account for geographic differences, site-regions were included as a factor in both the BRT algorithms and the regression models. Other potential covariates included:

- Demographic information (age, sex, race, ethnicity)
- Geographic information (hospital size, hospital type, urban/rural classification)
- High-risk medical conditions (cardiovascular disease, COPD, chronic lung disease, other pulmonary diseases, blood disorders, chronic metabolic disease, neurologic/neuromuscular disorders, immunocompromised conditions, hypertension, obesity, and others [Table S21])

Stratification

COVID-19 VE was also assessed by stratifying on potential effect modifiers including age group, race, ethnicity, high-risk status, and vaccine manufacturer. All stratified VEs were estimated by subsetting the data into categories of the potential modifier. Stratified VE estimates were assessed using the same approach detailed for the primary analysis. Variables for inclusion were first identified in the unstratified analyses. Then propensity score weights and VE estimates were calculated using only those events which qualify for the inclusion in the strata. Due to smaller sample size and date of FDA emergency use authorization, VE analysis by Johnson and Johnson (J&J) manufacturer incorporated four changes: (1) study start date began on the index date of first fully vaccinated J&J recipient for each respective partner, (2) any partners with fewer than five J&J vaccine recipients at the time of data collection were excluded from the analysis, (3) site-regions were grouped so that each region contained at least five J&J vaccine recipients, and (4) all underlying medical conditions were collapsed into two categories, non-respiratory or respiratory medical conditions.

Table S21. ICD-9 and-10 codes used for underlying medical conditions

Disease Condition	ICD-10 Codes	ICD- 9 Codes
Respiratory Disease:		
Asthma	J45.*	493.*
COPD	J40.*, J41.*, J42.*, J43.*, J44.*	491.*, 492.*, 496.*
Other Chronic Lung Disease	D86.0, E84.*, E88.01, J47.*, J60.*, J61.*, J62.*, J63.*, J64.*, J65.*, J66.*, J67.*, J68.*, J69.*, J70.*, J81.*, J82.*, J84.*, J95.0*, J96.*, J98.1*, J99.*, P25.*, P26.*, P27.*, P28.*, Q33.*, T86.3*, T86.8*, Z94.2, B39.*, B40.*, B41.*, B44.*, B45.*, B46.0, A15.*, A31.0, Q20.*, Q21.*, Q22.*, Q23.*, Q24.*, Q25.*, Q26.*, Q27.0, Q27.3*, Q27.4, Q27.8, Q27.9, Q28.*, Q89.3,	031.0*, 135.*, 277.0*, 273.4, 277.6*, 494.*, 495.*, 500.*, 501.*, 502.*, 503.*, 504.*, 505.*, 506.*, 508.*, 510.*, 513.*, 514.*, 515.*, 516.*, 517.*, 518.1*, 518.2*, 518.3*, 518.6*, 518.83, 519.9*, 519.0*, 748.4*, 748.5*, 748.6*, 759.3*, 770.2*, 770.7*, V42.6*, 714.81, 769.*, 770.*, 115.*, 116.*, 484.6, 117.3, 518.6, 117.5, 321.*, 117.7, 011.*, 012.*
Heart Disease:		
Heart Failure	I50.*	428.*
Ischemic Heart Disease	I21.*, I22.*, I23.*, I24.*, I25.*	410.*, 411.*, 412.*, 414.*
Hypertension	I10.*, I11.*, I12.*, I13.*, I15.*	401.*, 402.*, 403.*, 404.*, 405.*
Other Heart Disease	I01.*, I02.*, I05.*, I06.*, I07.*, I08.*, I09.*, I11.*, I13.*, I26.*, I27.*, I28.*, I31.*, I34.*, I35.*, I36.*, I37.*, I41.*, I42.*, I43.*, I44.*, I46.*, I48.*, I51.*, I52.*, I97.0, I97.1*, M31.*, Z94.1, Z95.*, Z98.61, I71.*, I72.*, I73.*, I74.*, I75.*, I79.*	393.*, 394.*, 395.*, 396.*, 397.*, 398.*, 415.*, 416.*, 417.*, 423.*, 424.*, 425.*, 426.*, 427.1*, 427.2*, 427.3*, 427.4*, 427.5*, 427.6*, 427.8*, 429.*, 440.*, 446.*, V42.1*, V45.0*, V45.81, V45.82, 997.1, 441.*, 442.*, 443.*, 444.*, 447.*, 446.1
Cerebrovascular Disease:		
Stroke	I60.*, I61.*, I63.*	430.*, 431.*, 433.*, 434.*
Other Cerebrovascular Disease	I62.*, I68.*, I69.*	432.*, 435.*, 436.*, 437.*, 438.*
Metabolic Disease:		
Diabetes Type I	E10.*	250.01, 250.03, 250.11, 250.13, 250.21, 250.23, 250.31, 250.33, 250.41, 250.43, 250.51, 250.53, 250.61, 250.63, 250.71, 250.73, 250.81, 250.83, 250.91, 250.93
Diabetes Type II	E11.*	250.02, 250.00, 250.12, 250.10, 250.22, 250.20, 250.32, 250.30, 250.42, 250.40, 250.52, 250.50, 250.62, 250.60, 250.72, 250.70, 250.82, 250.80, 250.92, 250.90
Diabetes due to underlying condition or other specified diabetes	E08.*, E09.* E13.*	251.* 357.2*, 362.0*, 362.11, 366.41
Other Metabolic Disease	E00.*, E01.*, E03.*, E05.*, E06.*, E15.*, E16.*, E20.*, E21.*, E22.*, E23.*, E24.*, E25.*, E26.*, E27.*, E28.*, E29.*, E31.*, E32.*, E34.*, Z68.4*, E70.*, E71.*, E72.*, E74.*, E75.2*, E76.*, E77.*, E78.*, E79.*, E80.*, E83.*, E85.*, E88.*	249*, 255.*, 270.*, 271.*, 272.*, 277.*
Other Diseases:		

Clinical Obesity	E66.*	278.*
Clinically Underweight	R63.6, F50.0*, E40.*, E41.*, E42.*, E43.*, E44.*, E45.*, E46.*	783.22, 307.1, 260.*, 261.*, 262.*, 263.*
Renal Disease	I12.*, I13.* N01.*, N02.*, N03.*, N04.*, N05.*, N06.*, N07.*, N08.*, N11.*, N14.*, N15.*, N16.*, N18.*, N25.*, N26.*, N28.*, Q27.1, Q27.2, Q60.*, Z49.*, Z91.15, Z94.0, Z99.2	285.21, 403.*, 404.*, 581.*, 582.*, 583.*, 585.*, 587.*, 588.0*, 588.1*, 590.0* 593.8.*, V42.0*, V56.*, V45.1*
Liver Disease	B18.*, I81.*, I85.*, K70.*, K71.*, K72.*, K73.*, K74.*, K75.*, K76.*, K77.*	571.*, 572.1*, 572.2*, 572.3*, 572.4*, 572.5*, 572.6*, 572.7*, 572.8*
Blood Disorder	D55.*, D56.0, D56.1, D56.2, D56.4, D56.5, D56.9, D57.0*, D57.1, D57.2*, D57.4*, D57.8*, D58.*, D59.*, D60.*, D61.*, D64.0, D64.1, D64.2, D64.3, D64.4, D64.8*, D65.*, D66.*, D67.*, D68.*	282.*, 283.*, 284*
Other Immunosuppression	B20.*, B59.*, B97.3*, D47.Z1, D70.*, D71.*, D72.*, D73.*, D76.*, D80.*, D81.*, D82.*, D83.*, D84.*, D89.*, M05.*, M06.*, M07.*, M08.*, M30.*, M31.*, M32.*, M33.*, M34.*, M35.0*, M35.9, Q89.0*, Z21*, Z51.0, Z51.1*, Z79.5*, Z79.82	042.*, 43.*, 44.*, 136.3*, 279.*, 288.0*, 288.1*, 288.2*, 288.4*, 446.*, 710.0*, 710.1*, 710.2*, 710.3*, 710.4*, 714.*, V08.*, V58.0*, V58.1*, 996.8.*, 710.*, 963.1
Organ Transplant	Z48.2*, Z94.*	V42.2*, V42.7*, V42.8*, V42.9*, V42.1*, V42.6*, V42.0*, V42.4,
Cancer	C00.*, C01.*, C02.*, C03.*, C04.*, C05.*, C06.*, C07.*, C08.*, C09.*, C10.*, C11.*, C12.*, C13.*, C14.*, C15.*, C16.*, C17.*, C18.*, C19.*, C20.*, C21.*, C22.*, C23.*, C24.*, C25.*, C26.*, C30.*, C31.*, C32.*, C33.*, C34.*, C37.*, C38.*, C39.*, C40.*, C41.*, C43.*, C44.*, C45.*, C46.*, C47.*, C48.*, C49.*, C4A.*, C50.*, C51.*, C52.*, C53.*, C54.*, C55.*, C56.*, C57.*, C58.*, C60.*, C61.*, C62.*, C63.*, C64.*, C65.*, C66.*, C67.*, C68.*, C69.*, C70.*, C71.*, C72.*, C73.*, C74.*, C75.*, C76.*, C77.*, C78.*, C79.*, C7A.*, C7B.*, C80.*, C81.*, C82.*, C83.*, C84.*, C85.*, C86.*, C88.*, C90.*, C91.*, C92.*, C93.*, C94.*, C95.*, C96.*, D03.*, D46.*	140.*, 141.*, 142.*, 143.*, 144.*, 145.*, 146.*, 147.*, 148.*, 149.*, 150.*, 151.*, 152.*, 153.*, 154.*, 155.*, 156.*, 157.*, 158.*, 159.*, 160.*, 161.*, 162.*, 163.*, 164.*, 165.*, 166.*, 167.*, 168.*, 169.*, 170.*, 171.*, 172.*, 174.*, 175.*, 176.*, 177.*, 178.*, 179.*, 180.*, 181.*, 182.*, 183.*, 184.*, 185.*, 186.*, 187.*, 188.*, 189.*, 190.*, 191.*, 192.*, 193.*, 194.*, 195.*, 196.*, 197.*, 198.*, 199.*, 200.*, 201.*, 202.*, 203.*, 204.*, 205.*, 206.*, 207.*, 208.*
Dementia (including Alzheimer's)	F01.*, F02.*, F03.*, G30.*	290.*, 294.1*, 331.*
Neurological/Musculoskeletal Disorder	H49.81*, M12.0*, M36.0, E75.02, E75.19, E75.4, F71.*, F72.*, F73.*, F84.2, G10.*, G11.*, G12.*, G13.*, G14.*, G20.*, G21.*, G23.*, G24.*, G25.*, G26.*, G31.*, G32.*, G35.*, G36.*, G37.*, G40.*, G45.*, G46.*, G60.*, G61.*, G62.*, G63.*, G64.*, G70.*, G71.*, G73.*, G80.*, G81.*, G82.*, G83.*, G90.3, G91.*, G93.*, G94.*, G95.*, G99.2, P91.*, Q00.*, Q01.*, Q02.*, Q03.*, Q04.*, Q05.*, Q06.*, Q07.*, Q76.*, Q77.*, Q78.*, Q79.*, Q85.*, Q87.4*, Q91.*, Q92.*, Q93.*, Q96.*, R41.*, R53.2, R54.*	318.1*, 318.2*, 330.*, 332.*, 333.0*, 333.4*, 333.5*, 333.6*, 333.7*, 333.8*, 333.9*, 334.*, 335.*, 336.*, 340.*, 341.*, 342.*, 343.*, 345.*, 344.0*, 358.0*, 358.1*, 359.*, 756.1*, 756.3*, 756.4*, 756.5*, 756.6*, 768.5*, 780.3*, 780.72
Down's Syndrome	Q90.*	758.0

* Includes all sub-codes

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Section S4. Supplemental Bias Analysis

Bias from misclassification of exposure and outcome in COVID-19 VE estimated from a test-negative design

Introduction

VISION COVID-19 VE estimates are made using a test-negative case-control design (TND). Although several forms of bias may distort estimates of vaccine effectiveness derived from TND studies, there have been few attempts to quantify their magnitude. Bias can arise from numerous sources. Of particular concern for VISION COVID-19 VE studies is bias arising from misclassification of study participants due to errors in measurement of exposure or outcome status. The VISION VE methodology relies on retrieval of electronic vaccination records from Electronic Health records (EHRs) and state registries, and these sources may imperfectly capture vaccination status, leading to misclassification of exposure. Although the VISION VE methodology relies on molecular assays to determine outcome status, these assays may also be imperfect, leading to misclassification of outcome.

We sought to assess the approximate magnitude of potential biases in COVID-19 VE estimates derived from TND studies due misclassification of outcome status arising from use of imperfect diagnostic tests and misclassification of exposure status due to imperfect capture of COVID-19 vaccination from electronic records (i.e., electronic medical record-linked vaccine registries). To do this, we examined biases arising in a simulated case-control study of COVID-19 vaccine effects in adults.

Methods

Following methods of Ferdinands and Shay 2011, we created a simulated cohort of individuals and followed them through a simulated test-negative case-control study using a decision tree model that mimics the structure and outcomes of a COVID-19 VE TND study. In this simulated study,

as in our actual study, cases are adults hospitalized with COVID-19-like illness who test positive with a SARS-CoV2 diagnostic test ordered at discretion of the clinical provider and controls are those who test negative.

As depicted by the branches of the decision tree (Figure 1), study participants were assumed to be vaccinated with a user-specified probability. In the unvaccinated subset of participants, the probability of an individual becoming infected with symptomatic COVID-19 illness was specified as *p_COVID* and, in the vaccinated subset of participants, the probability of COVID-19 was assumed to be a function of the true underlying VE among infection [*p_COVID**(1-*VE*)]. Participants had user-specified probabilities of becoming hospitalized and of receiving a diagnostic test for COVID-19 given hospitalization. Diagnostic test results were either positive or negative depending on true disease status and sensitivity and specificity of the diagnostic test. Each tested participant was either a true positive or a false negative (if the participant truly had COVID-19) or a true negative or a false positive (if the participant truly did not have COVID-19). A participant who tested positive, whether a true positive or a false positive, was classified as an observed case, as would happen in an actual TND study. A participant who was not tested would be ineligible and excluded from the study. Vaccination status was assumed to be retrieved from an electronic vaccine documentation system with imperfect sensitivity and specificity, such that the observed vaccination status used in the calculation of VE could differ from true vaccination status. Using Monte Carlo methods, we simulated the total number of cases, the number of vaccinated cases, and the ratio of vaccinated to unvaccinated cases. This ratio multiplied by the ratio of unvaccinated to vaccinated controls gave the observed odds ratio; 1 minus the observed odds ratio gave the observed VE. Bias was the difference between true and

observed VE. Each simulated scenario was based on 10,000 model iterations, and calculations were conducted with @RISK software (Palisade Inc; Ithica NY).

Decision Tree Input Values

Our decision tree model required several inputs to simulate a TND study. These variables included probability of COVID-19, expected VE among symptomatic COVID-19 infection, likelihood of being hospitalized given symptomatic COVID-19 infection, likelihood of being tested for COVID-19 if hospitalized, characteristics of clinical diagnostic COVID-19 tests, and characteristics of the vaccination documentation system. For the two sources of bias that we are evaluating – misclassification of exposure due to imperfect vaccination status reporting and misclassification of outcome due to imperfect diagnostic tests – the relevant inputs are defined by a probability distribution—a summary of the possible values of the variable—based on results of literature review. For these variables, we used a Beta-PERT distribution, which is summarized by its minimum, maximum, and most likely values. To parameterize these Beta-PERT distributions, we selected values that matched the range of values and used the median value as the most likely value, based on the literature. Other model inputs were point estimates derived from a review of the relevant literature including results from surveillance of COVID-19 illness, randomized trials of COVID-19 vaccine effects, and/or empirical data from our COVID-19 VE TND study, as described below.

SARS-CoV2 diagnostic test characteristics

We described the characteristics of SARS-CoV2 diagnostic testing using sensitivity and specificity. To obtain estimates of clinical test sensitivity and specificity, we conducted a

literature review to define the performance characteristics of clinical molecular diagnostic tests for SARS-CoV-2 detection. We limited the reviews to RT-PCR-based molecular assays because our TND study methodology is limited to those assays. Results came primarily from a meta-analysis by Dinnes et al. (2020) supplemented by results of assays conducted internally at one of our study sites (personal communication, A. Steffens, Jan 2021). We found 18 estimates of the sensitivity of molecular SARS-CoV-2 assays (Table 1), ranging from 68% to 100%, with median of 96%. For the model, we defined sensitivity with a Beta-PERT distribution with minimum 0.68, maximum 1.0 and most likely value of 0.96. We found 13 estimates of specificity of molecular SARS-CoV-assays, with minimum of 92%, maximum of 100% and median of 100%. Based on these values, we parameterized specificity with a Beta-Pert distribution with minimum 0.92, maximum of 1.0 and most likely value of 1.0. Sensitivity and specificity of these molecular tests were negatively correlated, and this correlation was accounted for in the model using correlation coefficient of -0.39.

Vaccine documentation characteristics

We described the characteristics of the COVID-19 vaccination documentation system using the sensitivity and specificity of the system. We conducted a literature review and contacted subject matter experts within the CDC COVID-19 response to identify reported performance characteristics of COVID-19 vaccination registries; however, no publications or unpublished results were identified. Hence, we conducted a literature review to establish performance characteristics of electronic influenza vaccination documentation systems as a proxy for COVID-19 systems. We found three studies reporting sensitivity of EHR- or vaccine registry-based documentation of influenza vaccination among adults and two studies reporting specificity of

these systems. In all of these studies, the electronic vaccination sources were compared to individual self-report as the gold standard. Electronic vaccination sources included EMRs and/or vaccine registries (we excluded studies evaluating billing data as a source of vaccine status). Based on three studies with five effect estimates (Sy 2010, Irving 2009, Greene 2009), sensitivity of vaccine documentation systems for influenza vaccine ranged from 68% to 95% with a median of 81% (Table 2). From two studies with four effect estimates, specificity ranged from 97% to 100% with a median of 98% (Sy 2010; Irving 2009) (Table 3). Sensitivity was parameterized with a Beta-Pert distribution with minimum 0.68, maximum 0.95 and most likely value of 0.81 for sensitivity, and specificity was parameterized with as a Beta-Pert distribution with minimum 0.97, maximum 1.0, and most likely value of 0.98.

Expected VE

Expected VE was assumed to be 95% based on the published estimates of vaccine efficacy of mRNA vaccines among RT-PCR–confirmed COVID-19 infection from randomized trials of COVID-19 vaccine among adults (Polack 2021; Baden 2021). In supplemental analyses, we lowered expected VE to 75% and 50%.

Vaccination coverage

Because vaccination rates can change rapidly, we conducted analyses using a wide range of vaccination coverage, from a low of 10% to a high of 90% vaccine coverage.

Probability of COVID-19 and hospitalization rates

We first built and calibrated the model based on data reflecting the period of time from June through September 2020, which was the period for which we could obtain information about

estimated COVID-19 attack rates from published sources. Specifically, we derived estimates of the probability of COVID-19 based on rates of symptomatic COVID-19 infection for adults ≥65 years provided from Reese et al.'s (2020) estimate of COVID-19 burden for the United States for the period of March through September 2020. This attack rate reflected adjustments for underreporting of COVID-19 cases and thus was considered to be a more accurate estimate of true COVID attack rates. From Reese's estimate, we derived a rate of COVID-19 illness of 0.0129 per month. This monthly rate was derived from the period of March through September because rates specifically from June to September were not available (hence, the monthly average rate from March to September was assumed to apply to the June to September time period). Percent COVID-19 positivity among patients observed in the simulated TND study was assumed to be 7%, the observed average percent of RT-PCR tests that were positive for SARS-CoV-2 for June through September, 2020 (personal communication, Situational Awareness Branch, COVID-19 Response, Feb 2021) and similar to the observed percent positive of 6.3% among adults aged ≥65 in our VISION VE study hospitals for the period from June through September, 2020 (personal communication, A. Steffens, Jan 2021). The likelihood of being hospitalized given symptomatic COVID-19 infection was assumed to be 22% for adults aged ≥65 years, based on the ratio of estimated hospitalizations to cases reported by Reese et al. Using these inputs, our model estimated a rate of COVID-19 hospitalization of 2.89 hospitalizations per 100,000 compared to Reese's 2.81 per 100,000. This scenario is referred to as the "lower burden scenario."

Because burden of COVID-19 illness varied during the period during which our VE estimate was derived (January to May 2021), we also estimated a "higher burden scenario" in which the

COVID-19 percent positivity in the hospital setting was assumed to be 25%, based on the observed positivity among our VISION VE study hospitals from January to March. The underlying probability of COVID-19 symptomatic illness was calibrated by increasing it to 0.074 per month to yield the observed 25% positivity.

SARS-CoV2 testing rate

The probability of clinical testing for SARS-CoV-2 given hospitalization for acute COVID-19-like respiratory illness was assumed to be 93%, the rate of testing observed for individuals ≥65 years of age at our VISION VE hospitals for the period of June through September 2020 (personal communication, A. Steffens, Jan 2021).

Bias estimate for pooled inpatient VE estimate

In addition to the scenarios described above, we evaluated potential bias for the pooled inpatient VE estimate assuming observed values for vaccine coverage, percent positivity, and testing rates. Values for these parameters were derived from the analytic dataset used to estimate pooled inpatient VE in the main manuscript.

Results

We first present results for the lower burden scenario in section 1, followed by the higher burden scenario in section 2. Finally, we summarize the bias estimate for the pooled inpatient VE estimate in section 3.

1. Lower burden scenario

1a. Expected VE = 95%

Imperfect test sensitivity. With imperfect test sensitivity only, observed VE was approximately 95%, and invariant with changes in vaccine coverage. Thus, bias in this scenario was essentially zero.

Imperfect test specificity. With imperfect test specificity only, observed VE was approximately 82%, and invariant with changes in vaccine coverage. Bias in this scenario was -13 percentage points from an expected VE of 95%.

Imperfect vaccine documentation sensitivity. With imperfect vaccine documentation sensitivity only, observed VE ranged from 95% at coverage of 10% to 87% at coverage of 90%. Bias in this scenario ranged from zero at low coverage to -8 percentage points from an expected VE of 95% at high coverage (Fig 2).

Imperfect vaccine documentation specificity. Observed VE ranged from 81% at coverage of 10% to 95% at coverage of 90%. Bias ranged from -14 percentage points at 10% coverage to essentially zero at 90% coverage (Fig 3).

Imperfect vaccine documentation and clinical tests. With both imperfect vaccine documentation and imperfect clinical tests, observed VE varied with coverage, with lower VE at the extremes of coverage (Fig 4). Bias ranged from -34 to -19 percentage points, depending on coverage.

1b. Expected VE = 75%

Imperfect test sensitivity. With imperfect test sensitivity only, observed VE was approximately 75%, and invariant with changes in vaccine coverage. Thus, bias in this scenario was essentially zero.

Imperfect test specificity. With imperfect test specificity only, observed VE was approximately 65%, and invariant with changes in vaccine coverage. Bias in this scenario was -10 percentage points from an expected VE of 75%.

Imperfect vaccine documentation sensitivity. With imperfect vaccine documentation sensitivity only, observed VE ranged from 75% at coverage of 10% to 53% at coverage of 90% (Fig. 5). Bias in this scenario ranged from zero at low coverage to -22 percentage points from an expected VE of 75% at high coverage.

Imperfect vaccine documentation specificity. Observed VE ranged from 64% at coverage of 10% to 75% at coverage of 90%. Bias ranged from -11 percentage points at 10% coverage to essentially zero at 90% coverage (Fig. 6).

Imperfect vaccine documentation and clinical tests. With both imperfect vaccine documentation and imperfect clinical tests, observed VE varied with coverage, with lower VE at the extremes of coverage and highest observed VE at coverage of around 40 to 50% (Fig 7). Bias ranged from -36 to -16 percentage points, depending on coverage.

1c. Expected VE = 50%

Imperfect test sensitivity. With imperfect test sensitivity only, observed VE was approximately 50%, and invariant with changes in vaccine coverage. Bias in this scenario was essentially zero.

Imperfect test specificity. With imperfect test specificity only, observed VE was approximately 43%, and invariant with changes in vaccine coverage. Bias in this scenario was -7 percentage points from an expected VE of 50%.

Imperfect vaccine documentation sensitivity. With imperfect vaccine documentation sensitivity only, observed VE ranged from 49% at coverage of 10% to 27% at coverage of 90% (Fig. 8).

Bias in this scenario ranged from -1 percentage point at low coverage to -23 percentage points from an expected VE of 50% at high coverage.

Imperfect vaccine documentation specificity. Observed VE ranged from 43% at coverage of 10% to 50% at coverage of 90% (Fig. 9). Bias ranged from -7 percentage points at 10% coverage to essentially zero at 90% coverage.

Imperfect vaccine documentation and clinical tests. With both imperfect vaccine documentation and imperfect clinical tests, observed VE varied with coverage, with lower VE at the extremes of coverage and highest observed VE at coverage of around 30 to 40% (Fig 10). Bias ranged from -12 to -29 percentage points, depending on coverage.

2. Higher burden scenario

2a. Expected VE = 95%

Imperfect test sensitivity. With imperfect test sensitivity only, observed VE was approximately 95%, and invariant with changes in vaccine coverage. Thus, bias in this scenario was essentially zero.

Imperfect test specificity. With imperfect test specificity only, observed VE was approximately 92%, and invariant with changes in vaccine coverage. Bias in this scenario was -3 percentage points from an expected VE of 95%.

Imperfect vaccine documentation sensitivity. With imperfect vaccine documentation sensitivity only, observed VE ranged from 95% at coverage of 10% to 88% at coverage of 90% (Fig. 11). Bias in this scenario ranged from zero at low coverage to -7 percentage points from an expected VE of 95% at high coverage.

Imperfect vaccine documentation specificity. Observed VE ranged from 81% at coverage of 10% to 95% at coverage of 90% (Fig. 12). Bias ranged from -14 percentage points at 10% coverage to essentially zero at 90% coverage.

Imperfect vaccine documentation and clinical tests. With both imperfect vaccine documentation and imperfect clinical tests, observed VE varied with coverage, with lower VE at the extremes of coverage and highest observed VE at coverage of around 40 to 60% (Fig 13). Bias ranged from -20 to -7 percentage points, depending on coverage.

2b. Expected VE = 75%

Imperfect test sensitivity. With imperfect test sensitivity only, observed VE was approximately 75%, and invariant with changes in vaccine coverage. Thus, bias in this scenario was essentially zero.

Imperfect test specificity. With imperfect test specificity only, observed VE was approximately 73%, and invariant with changes in vaccine coverage. Bias in this scenario was -2 percentage points from an expected VE of 75%.

Imperfect vaccine documentation sensitivity. With imperfect vaccine documentation sensitivity only, observed VE ranged from 75% at coverage of 10% to 53% at coverage of 90% (Fig. 14). Bias in this scenario ranged from zero at low coverage to -22 percentage points from an expected VE of 75% at high coverage.

Imperfect vaccine documentation specificity. Observed VE ranged from 64% at coverage of 10% to 75% at coverage of 90% (Fig. 15). Bias ranged from -11 percentage points at 10% coverage to essentially zero at 90% coverage.

Imperfect vaccine documentation and clinical tests. With both imperfect vaccine documentation and imperfect clinical tests, observed VE varied with coverage, with lower VE at the extremes of coverage and highest observed VE at coverage of around 40 to 50% (Fig 16). Bias ranged from -27 to -8 percentage points, depending on coverage.

2c. Expected VE = 50%

Imperfect test sensitivity. With imperfect test sensitivity only, observed VE was approximately 49%, and invariant with changes in vaccine coverage. Bias in this scenario was -1 percentage points from an expected VE of 50%.

Imperfect test specificity. With imperfect test specificity only, observed VE was approximately 49%, and invariant with changes in vaccine coverage. Bias in this scenario was -1 percentage points from an expected VE of 50%.

Imperfect vaccine documentation sensitivity. With imperfect vaccine documentation sensitivity only, observed VE ranged from 49% at coverage of 10% to 27% at coverage of 90% (Fig. 17). Bias in this scenario ranged from -1 percentage point at low coverage to -23 percentage points from an expected VE of 50% at high coverage.

Imperfect vaccine documentation specificity. Observed VE ranged from 43% at coverage of 10% to 50% at coverage of 90% (Fig. 18). Bias ranged from -7 percentage points at 10% coverage to essentially zero at 90% coverage.

Imperfect vaccine documentation and clinical tests. With both imperfect vaccine documentation and imperfect clinical tests, observed VE varied with coverage, with lower VE at the extremes of coverage and highest observed VE at coverage of around 40 to 50% (Fig. 19). Bias ranged from -25 to -7 percentage points, depending on coverage.

3. Bias estimate for pooled inpatient VE estimate

To illustrate the range of potential bias from misclassification of exposure and outcome relevant to the primary inpatient VE estimate, we used the model to estimate bias assuming observed values of COVID-19 percent positivity, COVID-19 testing rate (given hospitalization), and vaccination coverage.

The inpatient VE results presented in the main manuscript were derived within the context of 10% overall COVID percent positivity, testing rate of 74%, full mRNA vaccination coverage of 36%, and partial vaccination coverage of 14%. Assuming an expected VE of 95%, we estimated observed VE for full vaccination resulting from each source of bias that we modeled, separately and cumulatively (Table 4). For example, with imperfect sensitivity and specificity of clinical tests and imperfect vaccine documentation sensitivity and specificity, we would observe a VE of 85%.

Summary and Limitations

By simulating a test negative case-control study of COVID-19 VE in older adults, we found that misclassification of exposure and outcome, when considered together, led to underestimation of vaccine benefit. Our results aid interpretation of our VISION COVID-19 VE estimates by providing insight into the potential magnitude of underestimation of the VE estimates derived from our test-negative design study using molecular diagnostic assays and electronic vaccination documentation systems. For instance, assuming the inputs we specified and an expected VE of 95%, testing of 74%, percent positivity of 10%, and coverage of 36% for full vaccination (as

observed for the pooled inpatient VE mRNA estimate), we would expect to underestimate VE by about 10 percentage points due to misclassification of both exposure and outcome.

At low coverage, imperfect specificity of vaccine documentation was the largest contributor to underestimation of VE, suggesting that misclassification of COVID-19 vaccine status due to imperfect specificity may be an influential source of bias. Unfortunately, we had no empirical data about the specificity of the COVID vaccination documentation system and thus relied on information about influenza vaccination documentation. That literature, however, was also sparse, leaving considerably uncertainty about this value of specificity. Furthermore, the specificity values derived from the influenza literature were based on two studies that compared ascertainment of vaccination status by retrieval of electronic documentation with patient self-report of vaccination status. Because self-report is itself imperfect, we may have underestimated the specificity of the vaccine documentation system. For these reasons, it may be as plausible to assume 100% specificity of the electronic COVID vaccination documentation system (i.e., no false positives). Clearly it is important to obtain more and better information on the characteristics of the vaccine documentation system in order to improve our understanding of the approximate bias in VE. In lower burden scenarios, imperfect clinical test specificity also contributed substantially to bias. According to our simulations, imperfect sensitivity of clinical tests was not a meaningful contributor to bias of our VE estimates.

Although this supplemental analysis offers insight into potential bias by providing a quantitative estimate of the influence on VE from both misclassification of outcome and exposure, it has several limitations. The bias estimates should be interpreted with caution and are intended to

give an approximate idea of the magnitude of bias rather than precise estimates. Ours is a simple model of a test-negative design, and we did not model the potential attenuation of COVID-19 disease severity by vaccination. If vaccine attenuates the severity of disease, we expect VE among COVID-19 hospitalization to be higher than VE among symptomatic COVID-19 illness. Not every variable in our model was described by a probability distribution; hence, we did not represent all inherent uncertainty in model inputs. Some of the variables represented by probability distributions had little data upon which to base the distributions; in particular, as described above, we found no information about the performance characteristics of COVID-19 vaccine documentation systems and instead assumed performance characteristics of influenza vaccine documentation systems. Better information on the performance characteristics of COVID-19 vaccination documentation systems is needed. We assumed that misclassification of exposure and outcome were nondifferential, although this could be modified in future analyses. Thus, we would expect to observe bias toward the null, i.e., lower observed VE than expected VE, consistent with our findings. We focused on a VE study among older adults, and our results may not generalize to other age groups. Although we examined bias in VE estimates due to imperfect test characteristics and vaccine documentation, other sources of bias exist. Of importance are sources of potential selection bias that can distort estimates of VE. The over- or underestimation of VE arising from different types of selection bias should be systematically evaluated in future research.

The recommendation by the ACIP that all US adults receive COVID-19 vaccination likely means that future comparisons of COVID-19 outcomes in vaccinated and unvaccinated individuals in the United States will rely on observational studies. A better understanding of the

magnitude of potential biases in observational studies, particularly the commonly used test negative case-control studies, will be essential if we seek to monitor the effectiveness of the COVID-19 vaccine program.

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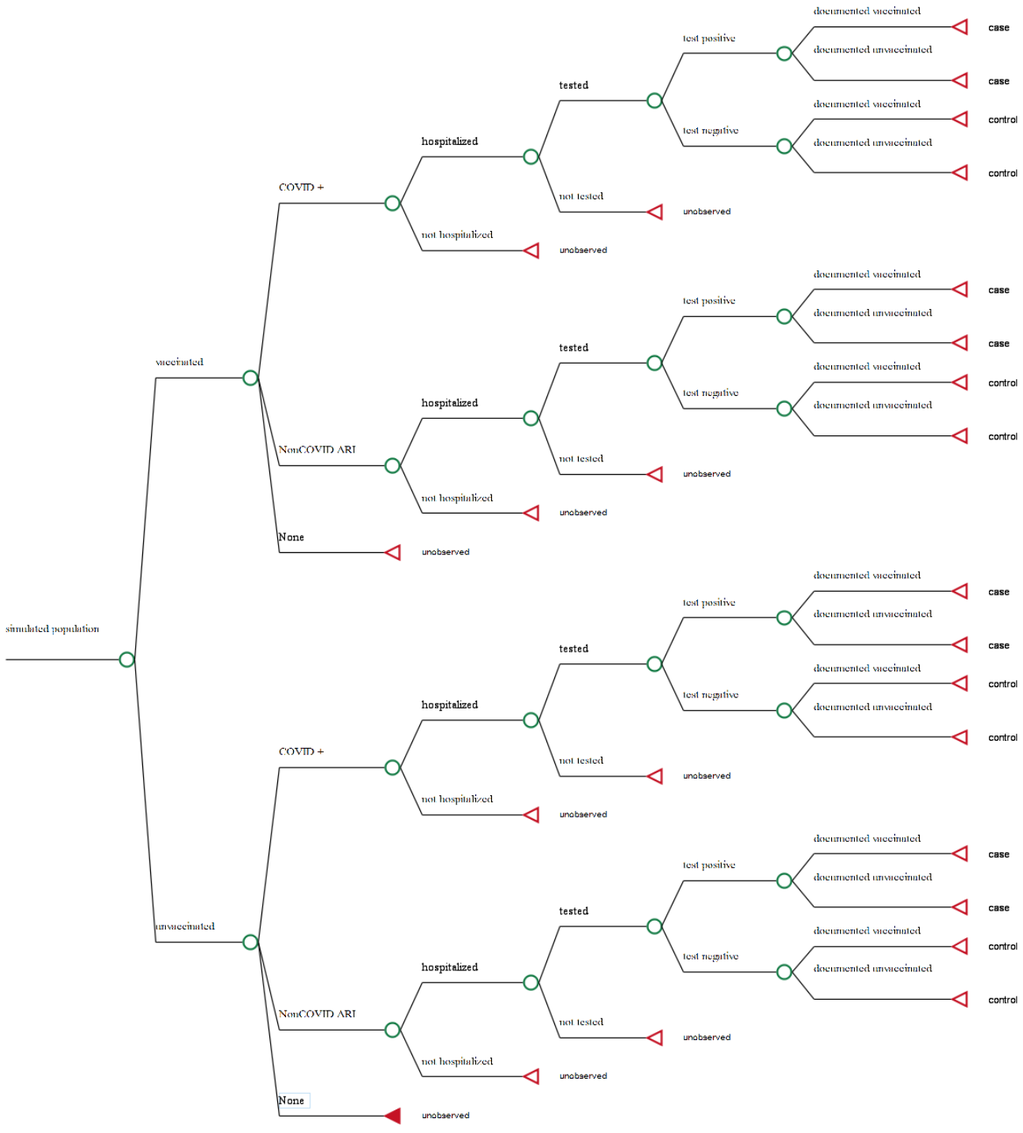
Acknowledgments

We thank Eric Griggs, Jeremiah Williams, and Palak Patel for help preparing this analysis.

Figures

Figure 1. Decision tree model for examining bias in estimates of vaccine effectiveness derived from a test-negative case-control study. Chance nodes are shown by circles, which denote outcomes that may occur by chance at each point in the tree. The likelihood of an outcome occurring is given by a user-specified probability and the probabilities of outcomes emanating from each chance node must sum to one. Terminal nodes (triangles) represent the observed study outcome.



EXPECTED VE = 95%, lower burden scenario

Figure 2. Observed VE with imperfect vaccine documentation sensitivity (expected VE = 95%); lower burden scenario

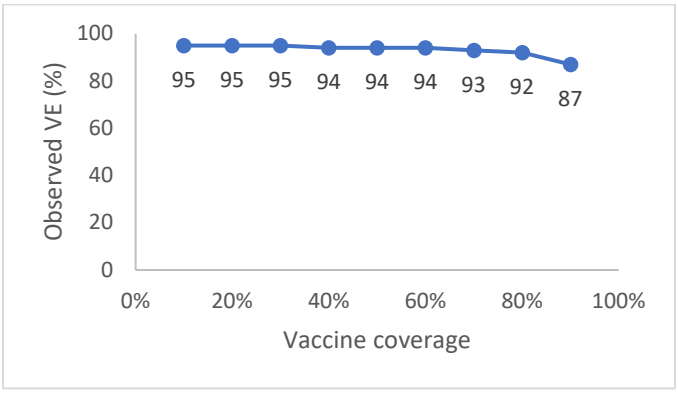


Figure 3. Observed VE with imperfect vaccine documentation specificity (expected VE = 95%); lower burden scenario

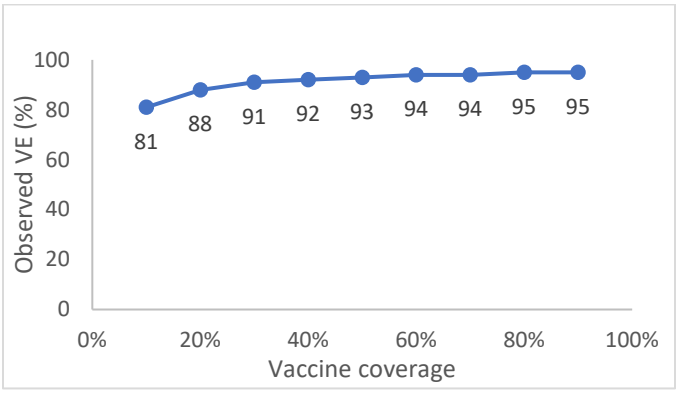
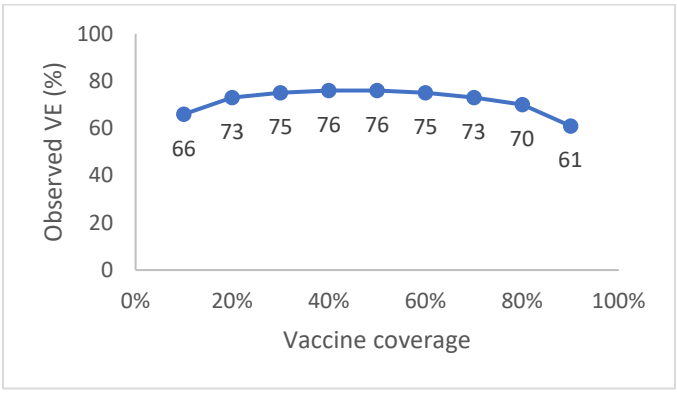


Figure 4. Observed VE with imperfect vaccine documentation and imperfect clinical tests (expected VE = 95%); lower burden scenario



EXPECTED VE = 75%, lower burden scenario

Figure 5. Observed VE with imperfect vaccine documentation sensitivity (expected VE = 75%); lower burden scenario

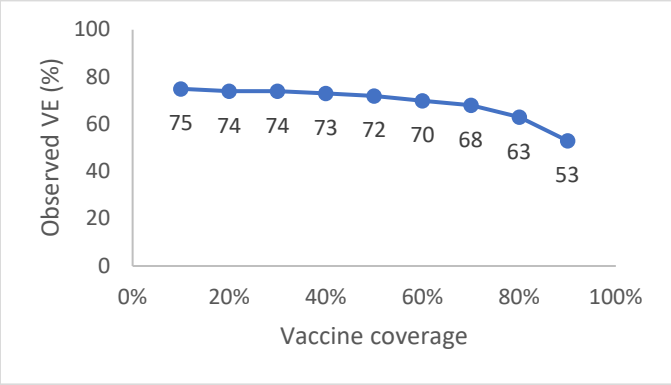


Figure 6. Observed VE with imperfect vaccine documentation specificity (expected VE = 75%); lower burden scenario

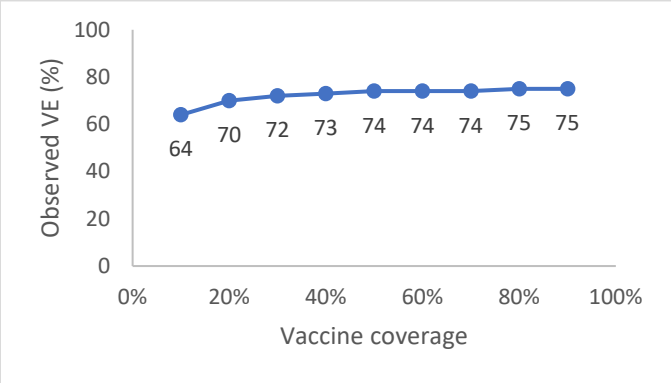
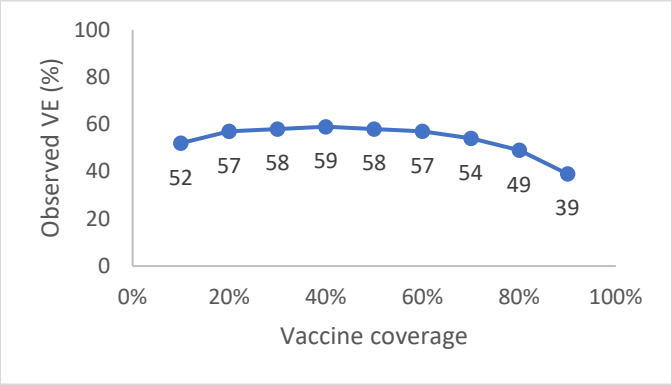


Figure 7. Observed VE with imperfect vaccine documentation and imperfect clinical tests (expected VE = 75%); lower burden scenario



EXPECTED VE = 50%, lower burden scenario

Figure 8. Observed VE with imperfect vaccine documentation sensitivity (expected VE = 50%); lower burden scenario

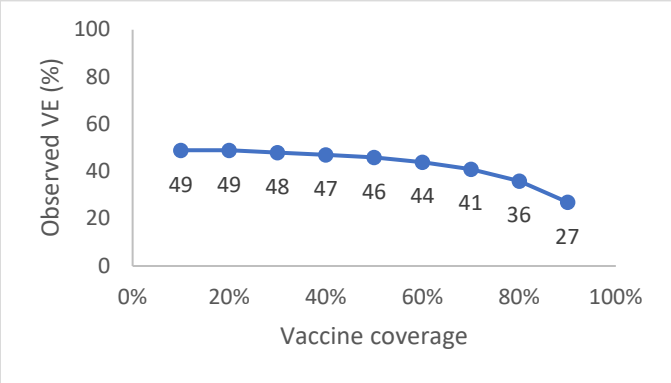


Figure 9. Observed VE with imperfect vaccine documenation specificity (expected VE = 50%); lower burden scenario

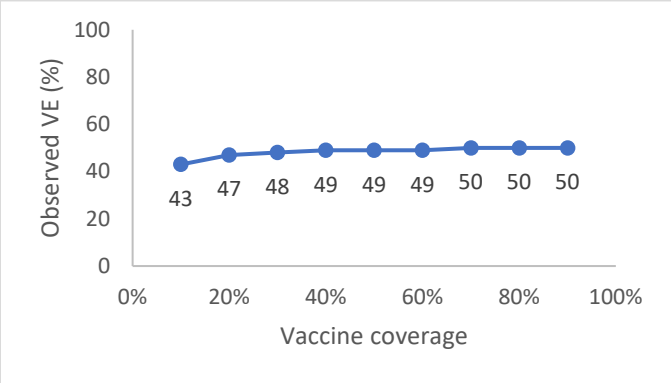
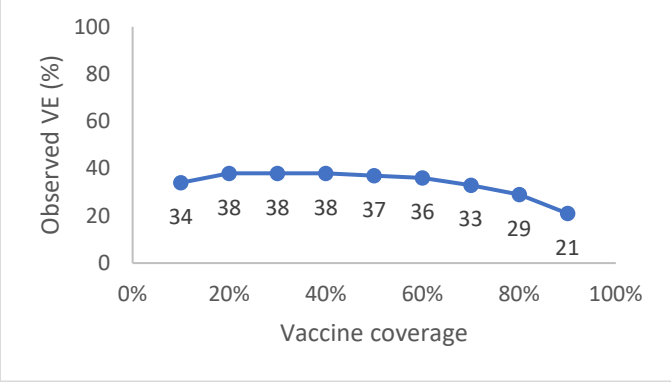


Figure 10. Observed VE with imperfect vaccine documentation and imperfect clinical tests (expected VE = 50%); lower burden scenario



EXPECTED VE = 95%, higher burden scenario

Figure 11. Observed VE with imperfect vaccine documenation sensitvity (expected VE = 95%); higher burden scenario

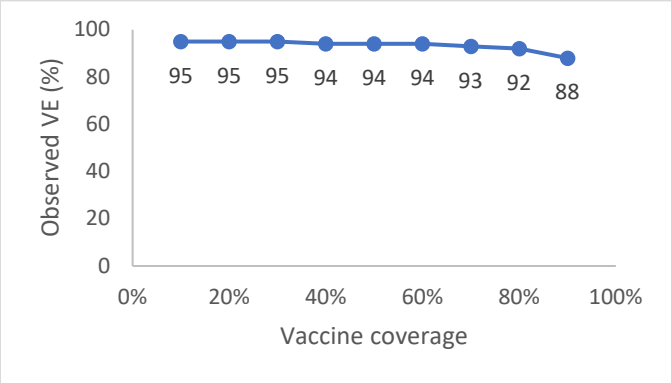


Figure 12. Observed VE with imperfect vaccine status specificity only (expected VE = 95%); higher burden scenario

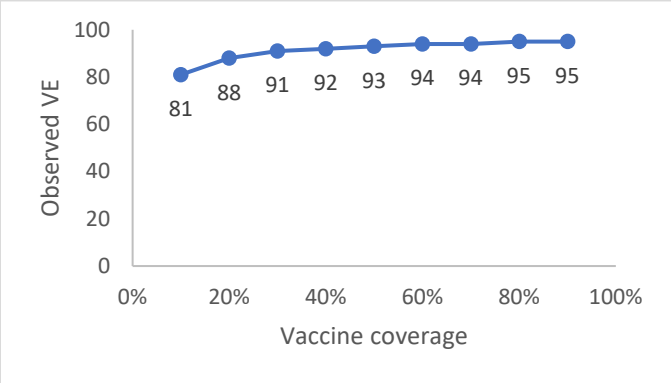
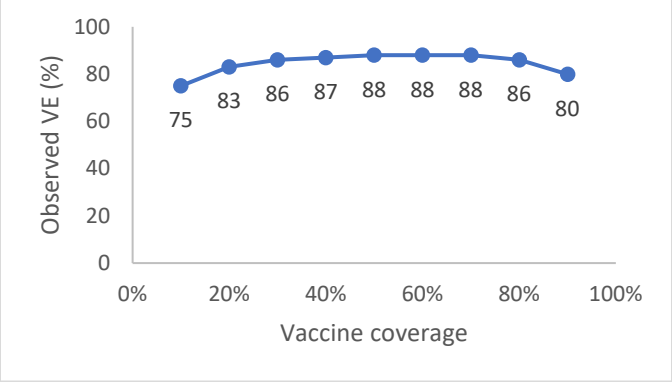


Figure 13. Observed VE with imperfect vaccine documentation and imperfect clinical tests (expected VE = 95%); higher burden scenario



EXPECTED VE = 75%, higher burden scenario

Figure 14. Observed VE with imperfect vaccine documentation sensitivity (expected VE = 75%); higher burden scenario

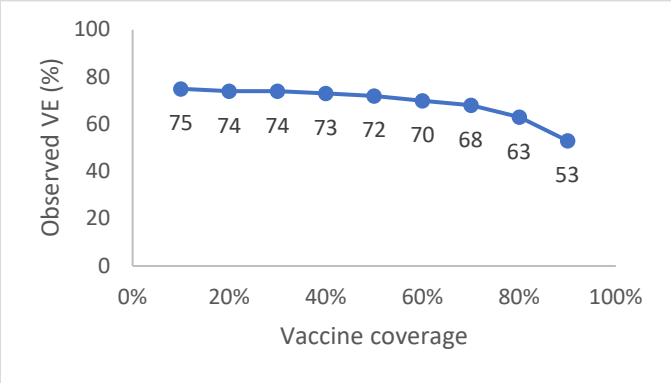


Figure 15. Observed VE with imperfect vaccine documenation specificity (expected VE = 75%); higher burden scenario

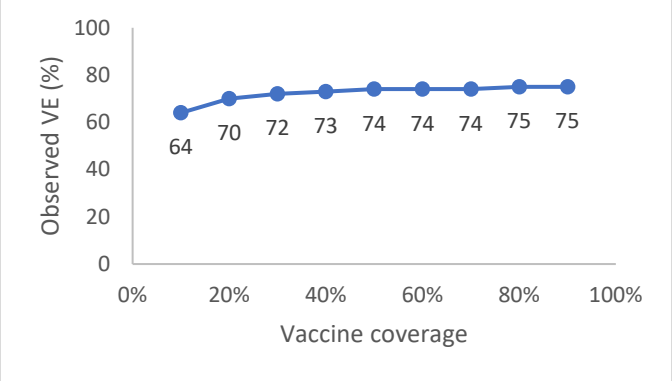
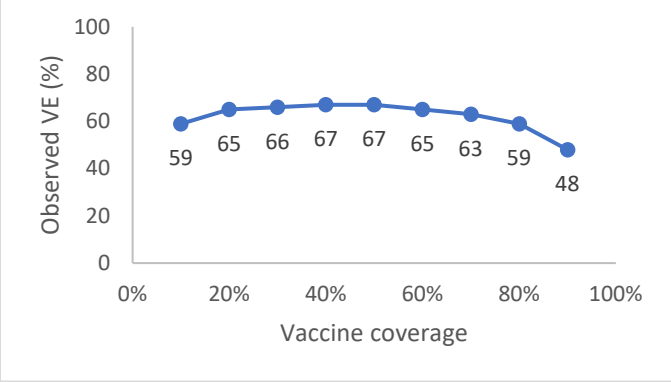


Figure 16. Observed VE with imperfect vaccine documentation and imperfect clinical tests (expected VE = 75%); higher burden scenario



EXPECTED VE = 50%, higher burden scenario

Figure 17. Observed VE with imperfect vaccine documentation sensitivity (expected VE = 50%); higher burden scenario

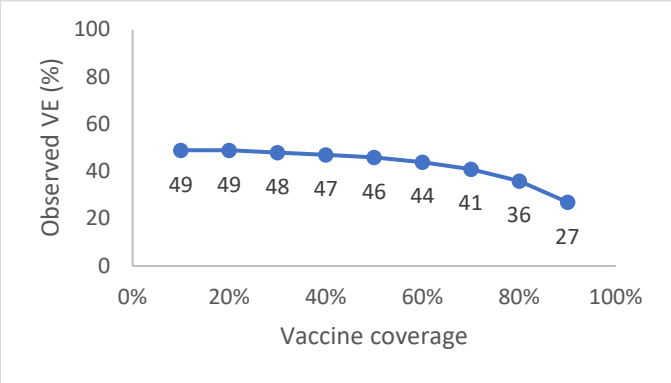


Figure 18. Observed VE with imperfect vaccine documentation specificity (expected VE = 50%); higher burden scenario

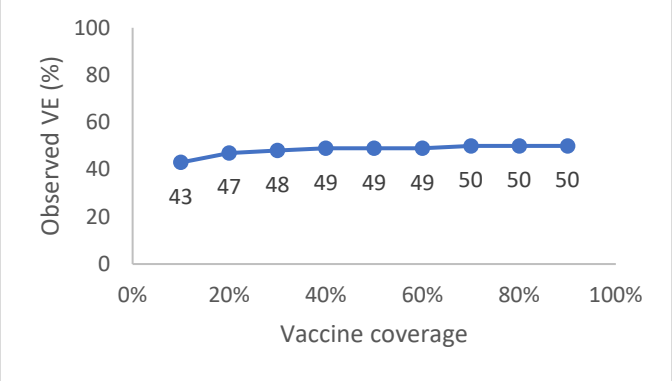
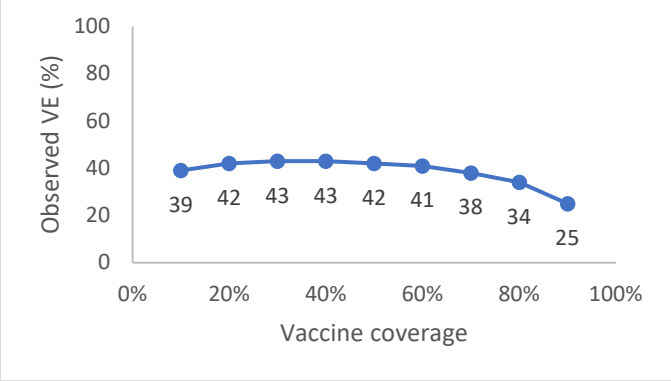


Figure 19. Observed VE with imperfect vaccine documentation and imperfect clinical tests (expected VE = 50%); higher burden scenario



Tables

Table 1. Performance of molecular and rapid molecular tests for detection of SARS-CoV-2

Source	Test assessed	Comparator	Type of specimen/swab	Sensitivity (95% CI)	Specificity (95% CI)
Dinnes 2020					
	1) ID NOW (Abbott laboratories)	RT-PCR			
	a. Smithgall 2020		mixed	0.74 (0.63, 0.83)	1.00 (0.86, 1.00)
	b. Rhoads 2020		mixed	0.94 (0.87, 0.98)	Not estimable
	c. Mitchell 2020		NP	0.72 (0.57, 0.84)	1.00 (0.78, 1.00)
	d. Moore 2020		NP	0.79 (0.71, 0.86)	1.00 (0.95, 1.00)
	e. Zhen 2020		NP	0.88 (0.76, 0.95)	1.00 (0.93, 1.00)
	f. Harrington 2020		nasal	0.75 (0.68, 0.81)	0.99 (0.98, 1.00)
	2) Xpert Xpress (Cepheid Inc)				
	a. Smithgall 2020		mixed	0.99 (0.94, 1.00)	0.92 (0.74, 0.99)
	b. Wolters 2020		mixed	1.00 (0.94, 1.00)	1.00 (0.88, 1.00)
	c. Moran 2020		mixed	1.00 (0.92, 1.00)	0.98 (0.91, 1.00)
	d. Broder 2020		NP	0.97 (0.85, 1.00)	Not estimable
	e. Zhen 2020		NP	0.98 (0.91, 1.00)	1.00 (0.93, 1.00)
	f. Lieberman 2020		NP	1.00 (0.75, 1.00)	1.00 (0.75, 1.00)
	g. Loeffelholz 2020		mixed	1.00 (0.97, 1.00)	0.96 (0.93, 0.98)
	3) Accula (Mesa Biotech Inc.)	RT-PCR	throat swab and nasal swab per test	0.68 (0.53, 0.81)	1.00 (0.93, 1.00)
	4) SAMBA II (Diagnotics for the Real World)	RT-PCR	combined nose and throat swabs, NP/OP swabs	0.99 (0.94, 1.00)	0.96 (0.90, 0.99)
KPNW Testing	1) Roche cobas SARS-CoV-2 & Influenza A/B	Hologic Aptima CoV-2 Assay	NP swab, nasal swab, nasal wash	1.00	1.00
	2) Cepheid Xpert Xpress SARS-CoV-2/Flu/RSV	Quidel Lyra Assay	NP swab, nasal wash	0.93	1.00
	3) Aptima SARS-CoV-2 Assay Hologic	Quidel Lyra and Cepheid	NP swab, nasal Swab	0.96	1.00

CI = confidence interval; NP = nasopharyngeal; OP = oral pharyngeal

Mixed = Any of the following swabs: NP swab, Nasal wash, OP swab, or throat swab

Table 2. Sensitivity of electronic sources of vaccination documentation for influenza vaccination compared to self-report as the gold standard

Source	Age group	Comparator	Sensitivity	95% LCL	95% UCL
Sy 2010	50-64 yr	EMR vs self-report	0.73	0.66	0.81
Sy 2010	65-79 yr	EMR vs self-report	0.86	0.80	0.92
Irving 2009	≥6 months	registry vs adjudicated self-report	0.95	0.93	0.96
Greene 2009	50-64 yr	electronic records vs self-report	0.68	0.65	0.71
Greene 2009	65-79 yr	electronic records vs self-report	0.81	0.79	0.83

EMR = electronic medical record; LCL = lower confidence limit; UCL = upper confidence limit

Table 3. Specificity of electronic sources of vaccination documentation for influenza vaccination compared to self-report as the gold standard

Source	Age group	Comparator	Specificity	95% LCL	95% UCL
Sy 2010	50-64 yr	EMR vs self-report	1.00	1.00	1.00
Sy 2010	65-79 yr	EMR vs self-report	0.98	0.94	1.00
Irving 2009	5-49 yr	registry vs self-report	0.99	0.98	0.99
Irving 2009	≥50 yr	registry vs self-report	0.97	0.94	0.99

EMR = electronic medical record; LCL= lower confidence limit; UCL = upper confidence limit

Table S4. Estimated observed VE for full vaccination assuming an expected VE of 95%

Sources of bias included	Observed VE for full vaccination (assuming expected VE = 95%)
Imperfect test sensitivity only	95%
Imperfect test specificity only	90%
Both imperfect test sensitivity and specificity	90%
Imperfect vaccine documentation sensitivity only	95%
Imperfect vaccine documentation specificity only	92%
Both imperfect vaccine documentation sensitivity and specificity	91%
Imperfect test sensitivity, imperfect test specificity, imperfect vaccine documentation sensitivity, imperfect vaccine documentation specificity	85%

Section S5. Supplemental Results (Other Results not in Main Manuscript)

A. Sample of Medical Encounters

1. Differences in medical event exclusions by Network partner

Graphics that illustrate the location of Network hospitals and ED/UC facilities are presented in Figure S11 and Figure S12. Breakdowns of the inclusion and exclusion steps by Network partner are presented in Table S3 for hospitalizations and in Table S5 for ED/UC. The proportion of hospitalizations that occurred after the dates of age-specific COVID-19 vaccine eligibility varied by partner, ranging from 28% at RG to 54% at KPNW. RG and IH excluded a higher proportion of hospitalizations due to the absence of molecular testing for SARS-CoV-2 within the eligible testing window (45% for RG and 40% at IH compared to a range of 1%-8% for other partners). HP had a higher percentage of encounters excluded for indeterminate vaccination status (9% for HP versus a range of 3%-6% for other partners). For the combined sample, 10% of hospitalizations occurred within 30 days of discharge and were combined into a single medical event; 0.6% of ED or UC encounters occurred within 24 hours and were combined into a single medical event.

Figure S11. VISION VE Map of Hospital Locations

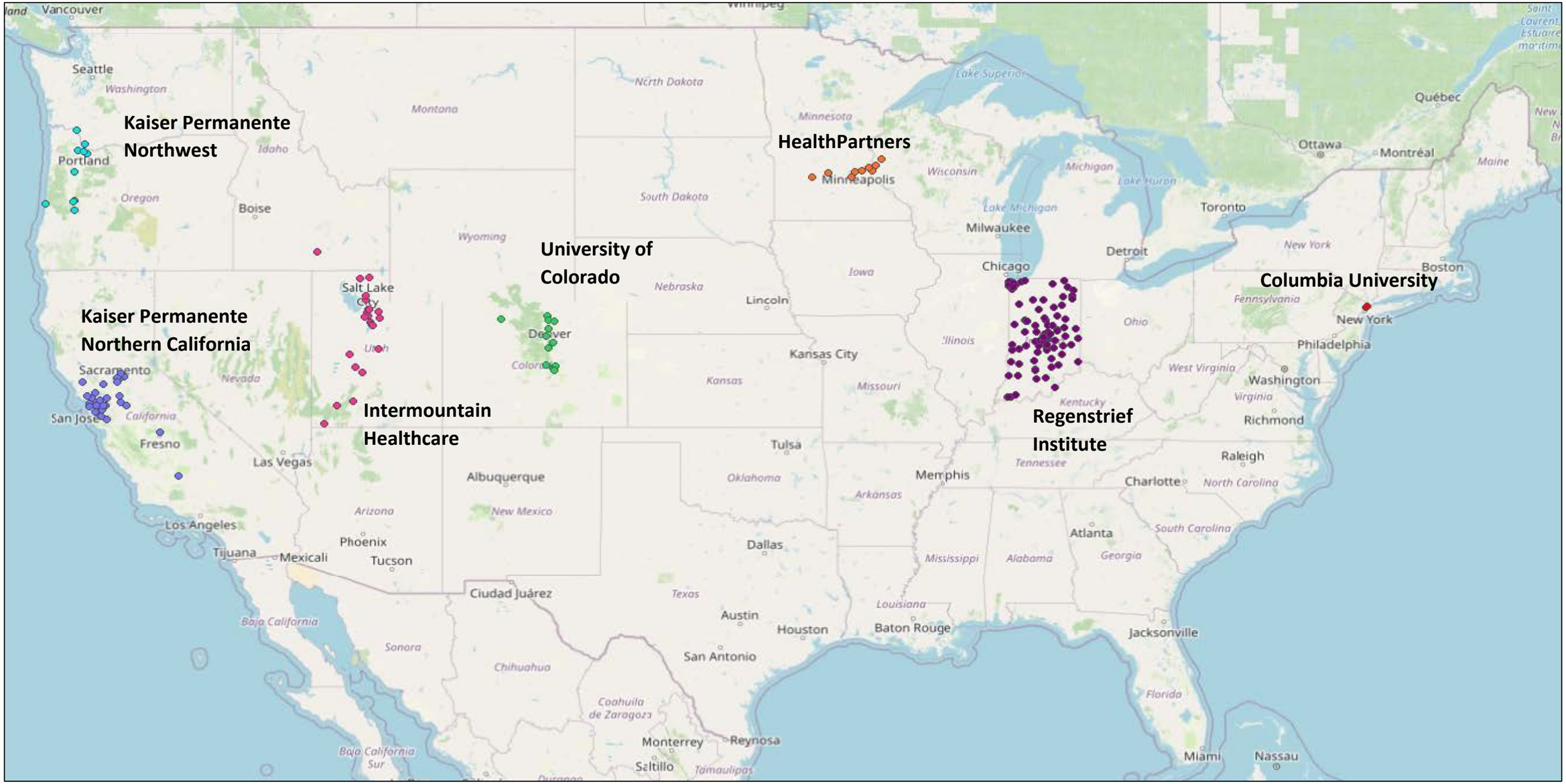
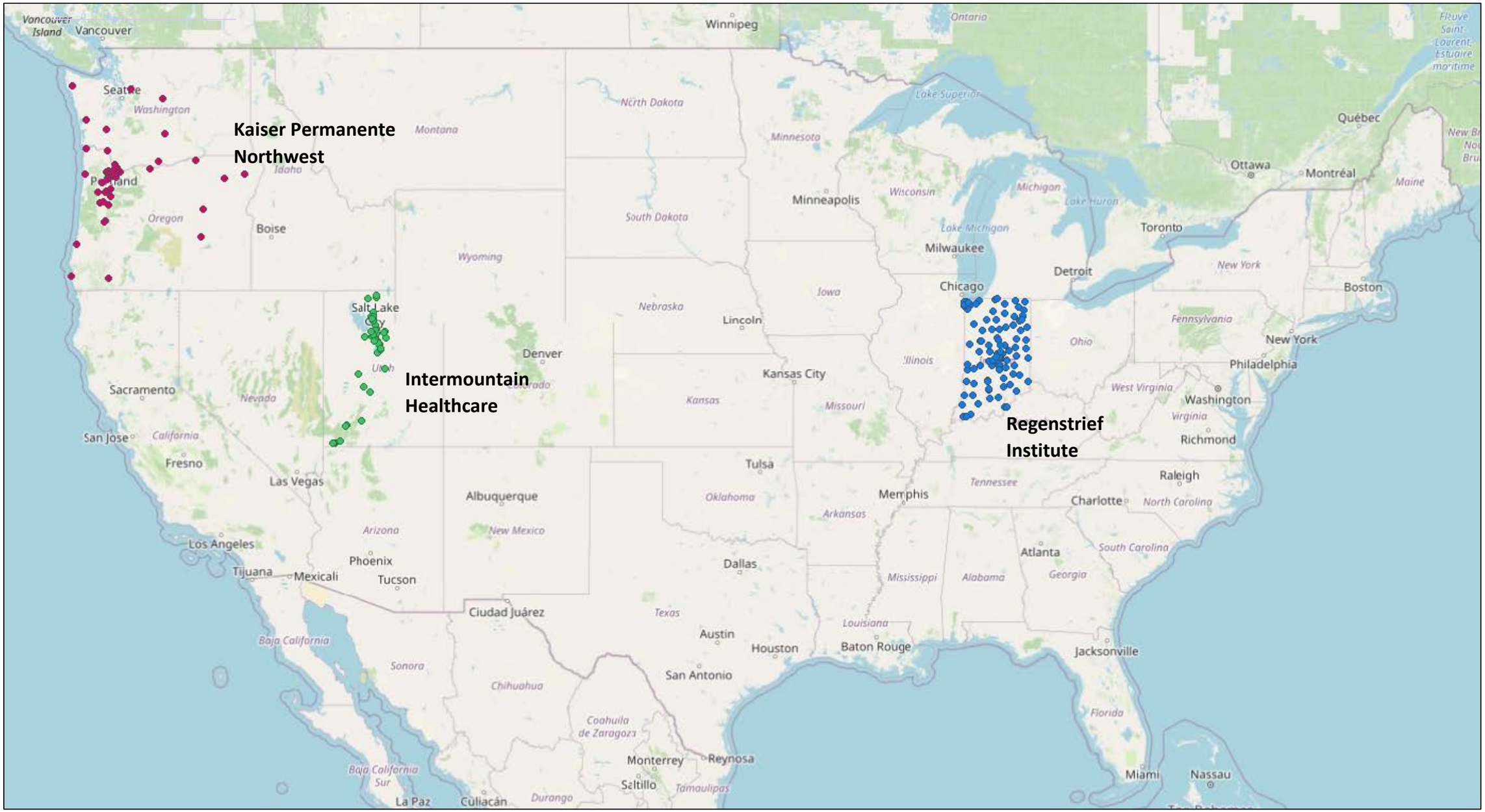


Figure S12. VISION VE Map of ED and UC facilities' Location



2. Differences in Race and Ethnicity by Network partner

All partners had inpatient populations that were majority White race (range = 56%-96%). The percentage of hospitalizations among Black patients was highest at CUIMC (42%), RG (13%) and KPNC (11%). The proportion of the patients who self-identified as Hispanic was highest at KPNC (20%) and CUIMC (55%) and was <10% for all other partners (range = 2%-10%). At CUIMC, a high proportion of inpatient encounters did not have a reported value for race (50% versus 2%-17% at other sites). See Tables_S6-S11 for partner-specific results.

Across all partners, the proportion of White patients increased with age in both the inpatient population (77% to 84% for those aged 50-64 and ≥85 years respectively) and ED/UC population (88% to 96% for those aged 50-64 and ≥85 years respectively). The proportion of Black patients decreased with age in both the inpatient population (16% to 8% for those aged 50-64 and ≥85 respectively) and ED/UC population (8% to 2% for those aged 50-64 and ≥85 years respectively). The proportion of the population that identifies as Hispanic decreased with age in the inpatient (16% to 12% for those aged 50-64 and ≥85 years respectively) and ED/UC populations (9% to 3% for those aged 50-64 and ≥85 years respectively) (data not shown).

3. COVID-19 Vaccine Products and Manufacturer

Proportions of vaccine manufacturer differed by site (Table S6-S11). The proportion of vaccinated encounters associated with Pfizer-BioNTech vaccine ranged from 42% at RG to 71% at CUIMC in the inpatient setting and from 43% at RG to 67% at KPNW in the ED/UC setting. RG was the only partner with more patients vaccinated with Moderna vaccine (55% of hospitalizations with a vaccinated patient and 53% of ED/UC encounters with a vaccinated patient) than Pfizer-BioNTech vaccine (42% and 43% respectively). All but one partner (UCO) had at least one encounter of an individual fully vaccinated with the J&J vaccine, ranging from 1% to 5% of vaccinated inpatient encounters and 4% to 5% of ED/UC encounters across partners.

B. Laboratory-confirmed COVID-19-associated Medical Encounters

The association between SARS-CoV-2 test results and patient characteristics are presented for the combined sample in Table 2 and for each Network partner in Table S6-S11. SARS-CoV-2 positivity declined with age among both hospitalized and ED/UC encounters; this was noted consistently across Network partners. The lower percentages of medical events that were SARS-CoV-2 positive among White or Other race patients, non-Hispanic patients, and those with non-respiratory chronic conditions noted for the combined sample were also noted across most but not all study partners when examined separately.

The vast majority (>88%) of CLI hospitalizations and ED/UC encounters associated with a SARS-CoV-2 positive test result corresponded to ≥1 clinical diagnosis ICD code in the hospital discharge or ED/UC medical record (by partner see Table S6-S11). The remaining ≤12% of medical events among SARS-CoV-2 positives were included in the sample because ≥1 ICD code for a sign or symptom associated with COVID-19 was listed for the event. In contrast, among SARS-CoV-2 negative medical events, 25,706/37,231 (69%) of hospitalizations and 8,740/18,271 (48%) of ED/UC encounters corresponded to ≥1 clinical diagnosis ICD code (by partner see Table S6-S11). Thus, a greater proportion of SARS-CoV-2 negative medical events were included because of CLI signs or symptoms compared to SARS-CoV-2 positive medical events. The potential that these differences may introduce bias in VE estimates is examined in VE sensitivity analyses that narrow the sample of encounters to those with similar clinical presentations as described below.

C. COVID-19 Vaccination Status

Among both hospital and ED/UC settings, the percentage with full (mRNA) vaccination was higher among older individuals and among those of White or other race (Table 2). These trends were noted across most but not all Network partners (Tables S6-S11).

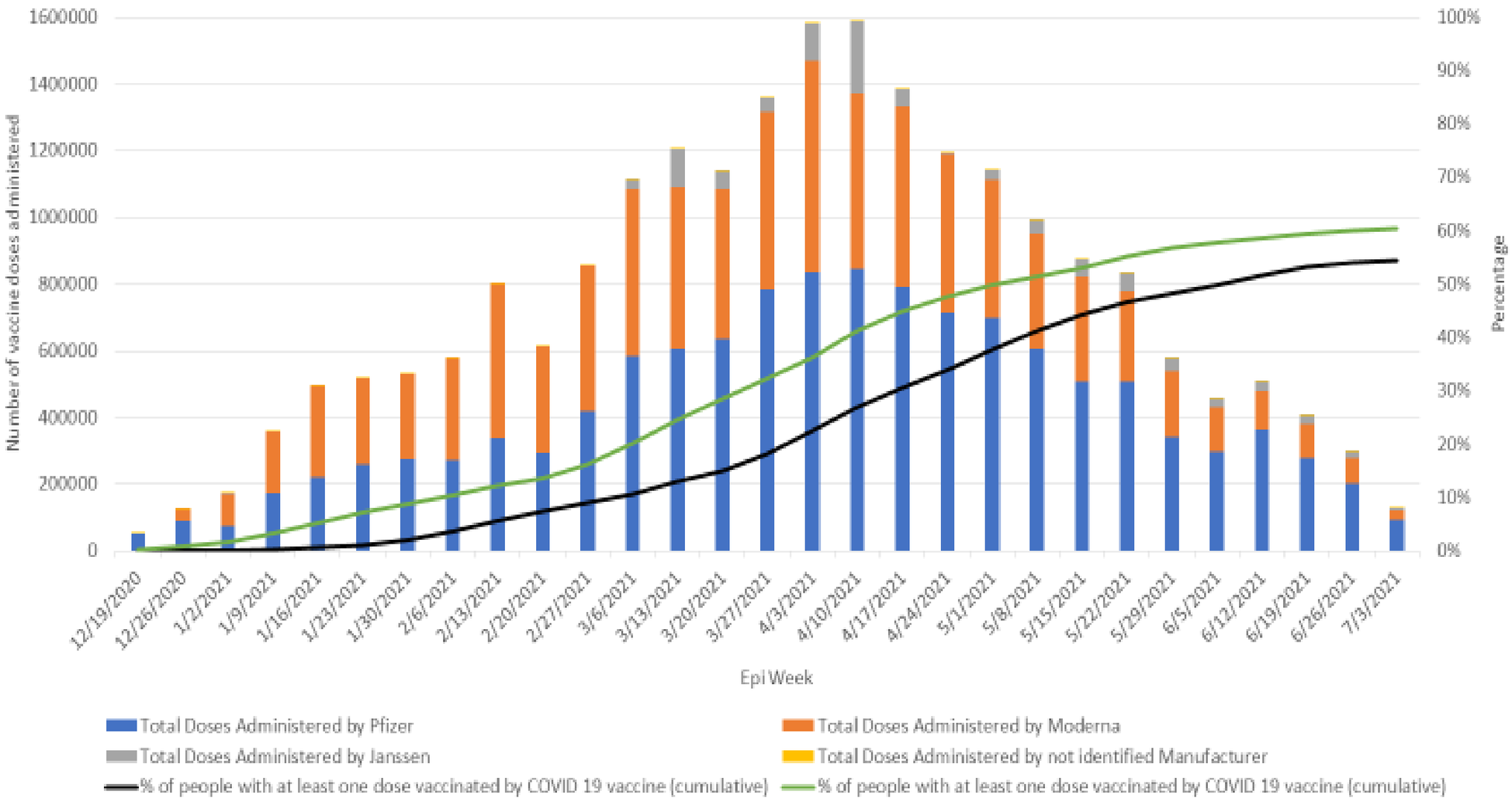
The median days (and IQR) from the most recent vaccination to the index date are listed in Table S4. As one would expect given that this evaluation occurs through June 22, 2021 and thus in the early weeks and months since COVID-19 vaccines became available to the public, a patient's index date was typically less than 2 months after their most recent vaccination date. For example, among COVID-19 cases who were fully vaccinated with a mRNA vaccine, the hospitalization index date was a median of 56 (IQR = 36-78) days after their 2nd dose of vaccine. The median days from vaccination to index date did not differ for SARS-CoV-2 positive cases versus SARS-CoV-2 negative controls.

Similarly, most unvaccinated patients had only been eligible for vaccine for less than 2 months. The median (IQR) days from vaccine eligibility to the index date was 38 (14-67) days among unvaccinated COVID-19 hospitalized patients and 40 (14-70) days among unvaccinated COVID-19 ED/UC patients.

Based on routine monitoring and reporting of vaccination by CDC in CDC COVID Data Tracker, the proportion vaccinated with at least 1 dose of COVID-19 vaccine varied by state, ranging from approximately 38% in Utah to 58% in California by the third week of May 2021. The proportion fully vaccinated for COVID-19 vaccine ranged from 26% in Utah to 44% in New York City. This information from unpublished CDC data is presented for each Network partner in Figures S13-S19.

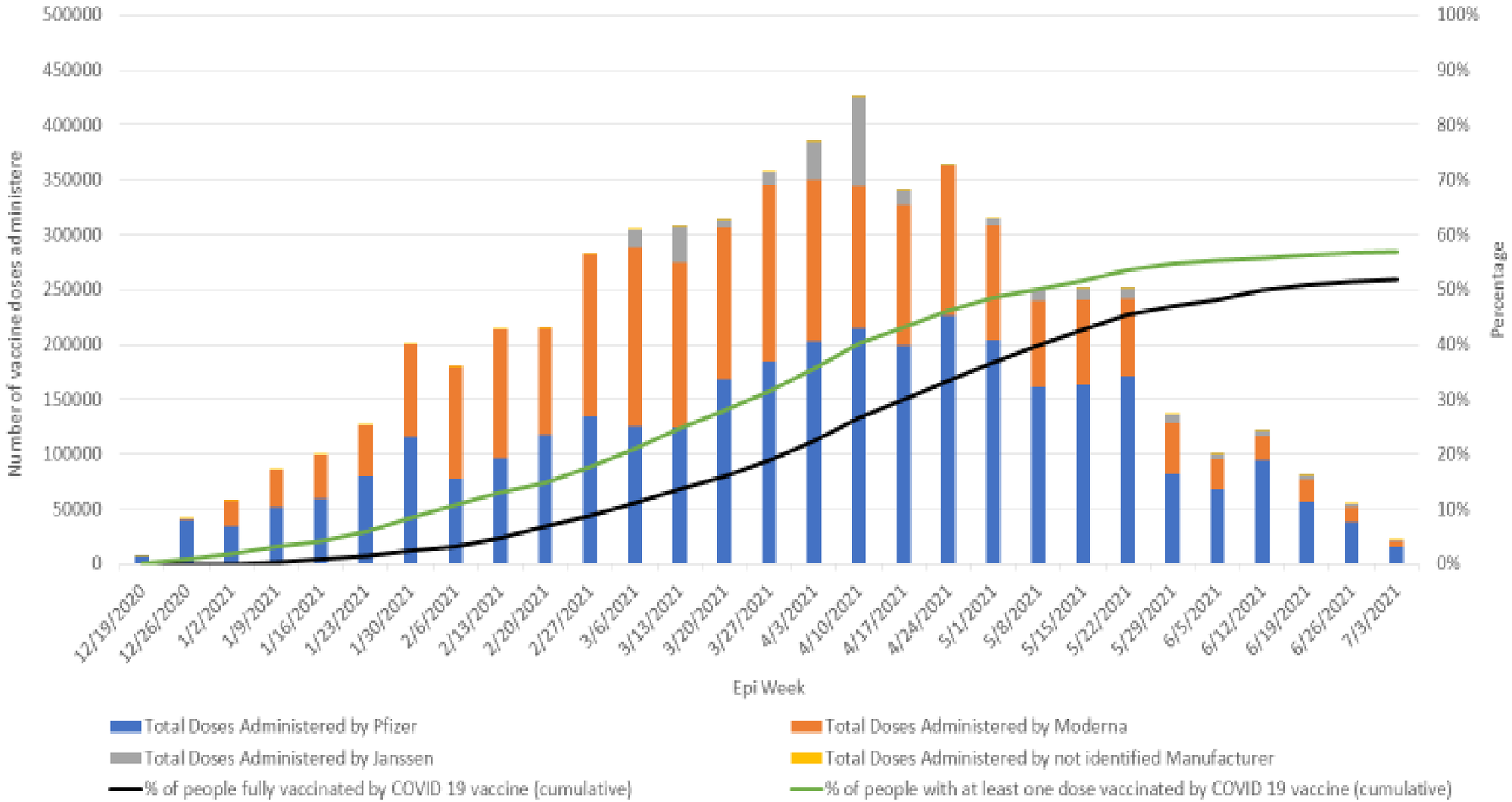
Figures S13-19. Statewide COVID-19 Vaccine Coverage Graphs – By State

Figure S13. Statewide Total Number of COVID-19 Vaccine Doses Administered and the Cumulative Percentage of People Fully and Partially Vaccinated by COVID-19 Vaccine, New York, December 19, 2020-July 2, 2021



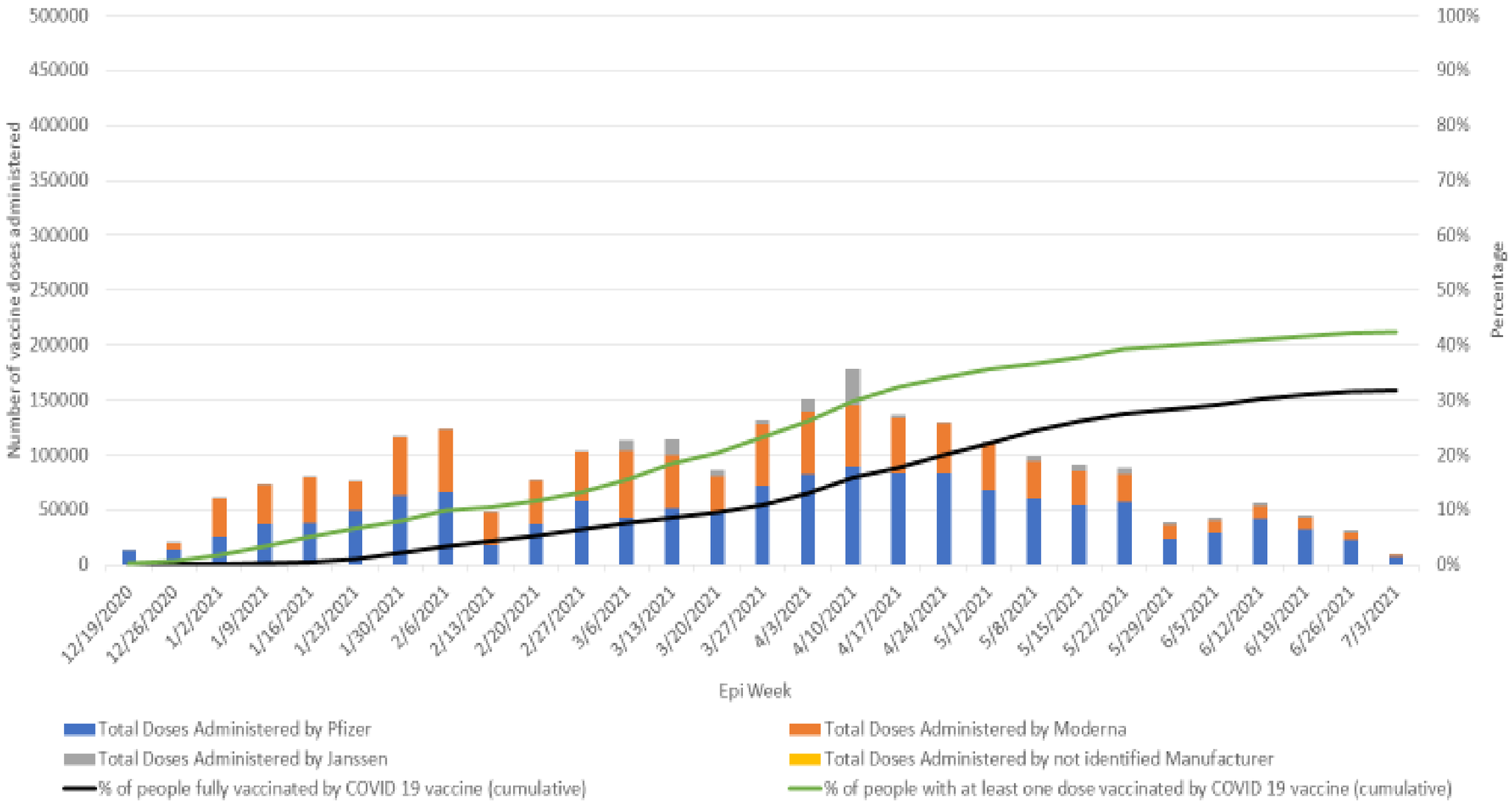
CDC, unpublished data, 2021. Data provided from the Routine Reporting and Data Visualization Team, Data Monitoring and Reporting Section, CDC Vaccine Task Force on July 2, 2021

Figure S14. Statewide Total Number of COVID-19 Vaccine Doses Administered and the Cumulative Percentage of People Fully and Partially Vaccinated by COVID-19 Vaccine, Minnesota, December 19, 2020-July 2, 2021



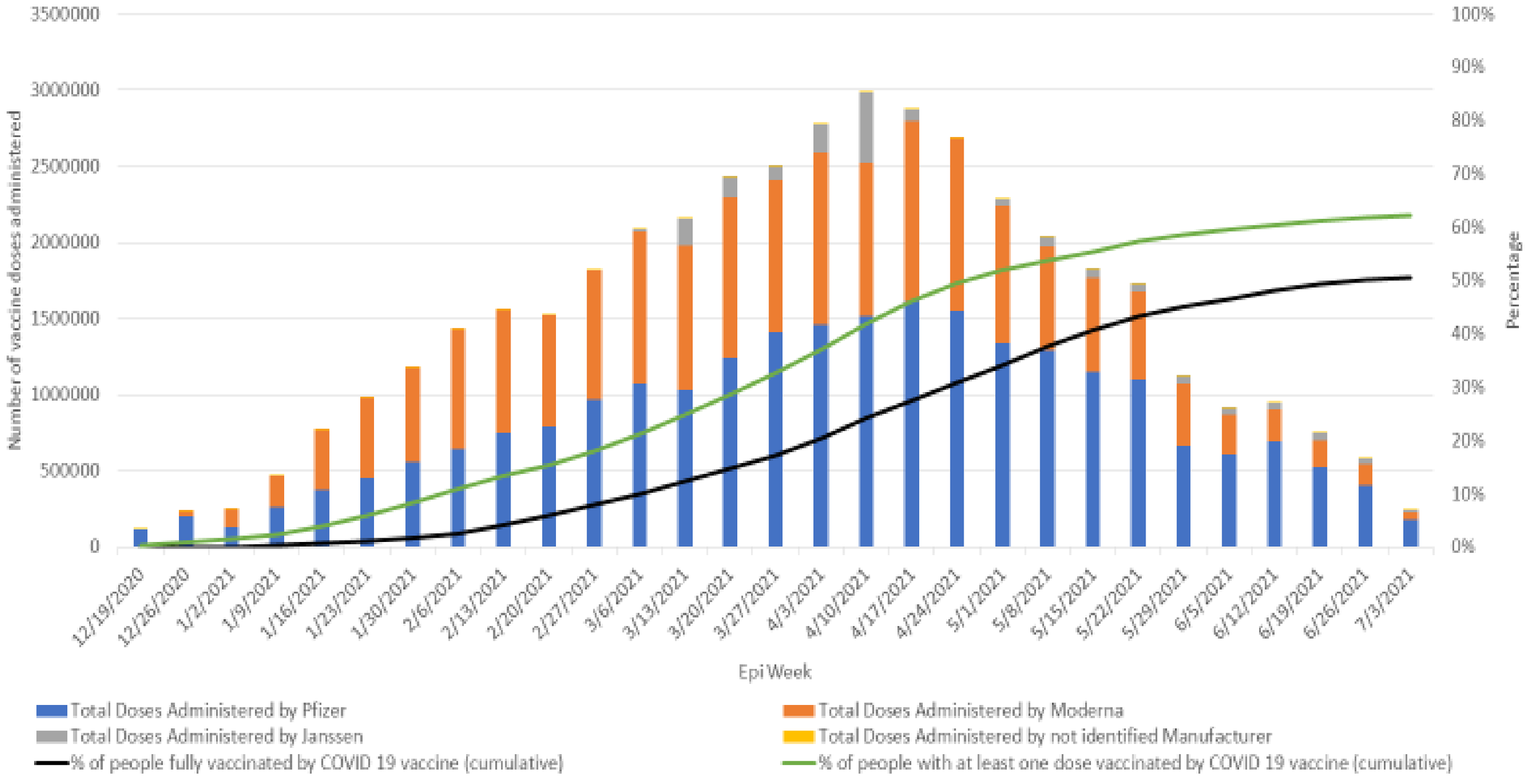
CDC, unpublished data, 2021. Data provided from the Routine Reporting and Data Visualization Team, Data Monitoring and Reporting Section, CDC Vaccine Task Force on July 2, 2021

Figure S15. Statewide Total Number of COVID-19 Vaccine Doses Administered and the Cumulative Percentage of People Fully and Partially Vaccinated by COVID-19 Vaccine, Utah, December 19, 2020-July 2, 2021



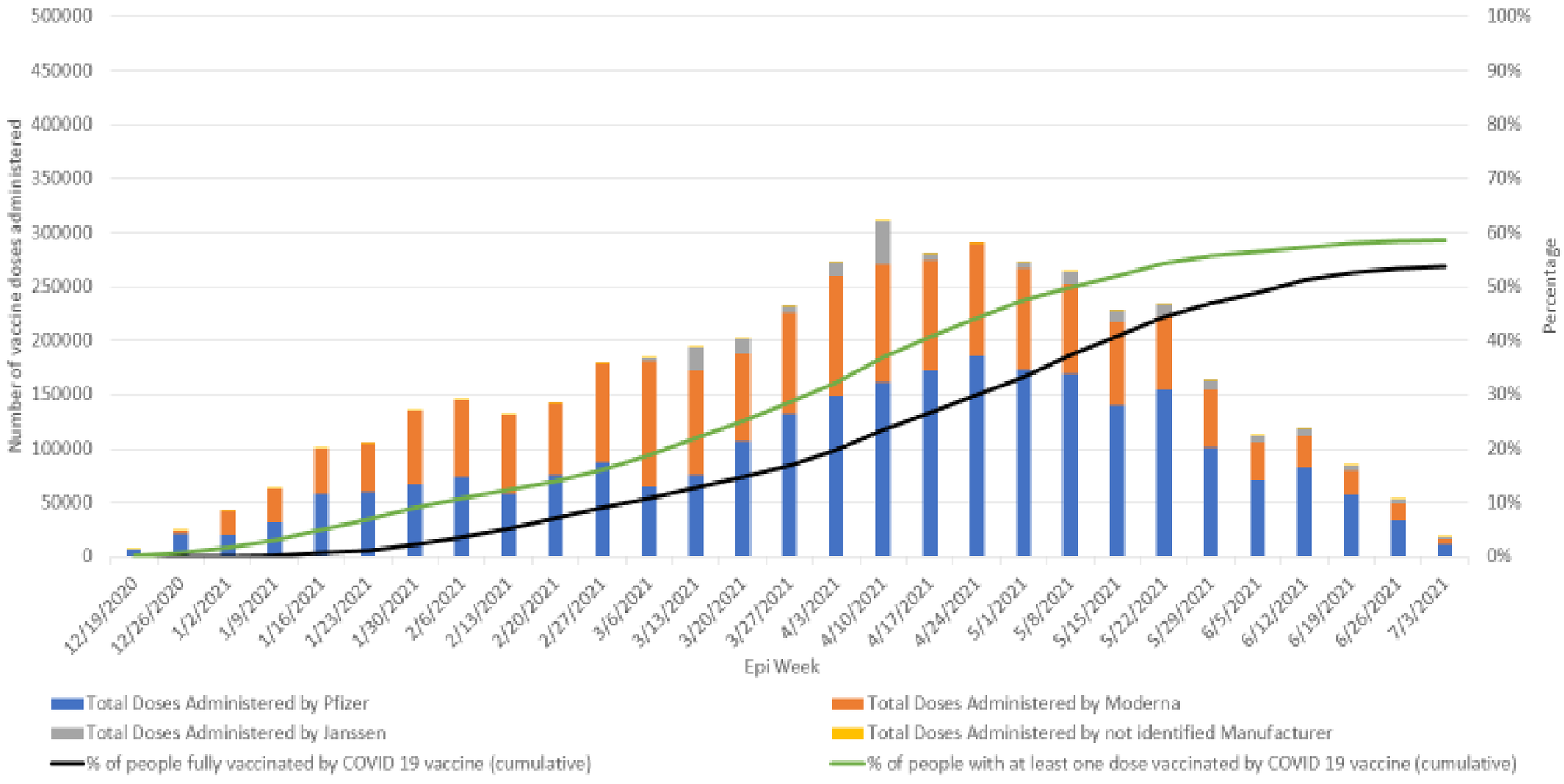
CDC, unpublished data, 2021. Data provided from the Routine Reporting and Data Visualization Team, Data Monitoring and Reporting Section, CDC Vaccine Task Force on July 2, 2021

Figure S16. Statewide Total Number of COVID-19 Vaccine Doses Administered and the Cumulative Percentage of People Fully and Partially Vaccinated by COVID-19 Vaccine, California, December 19, 2020-July 2, 2021



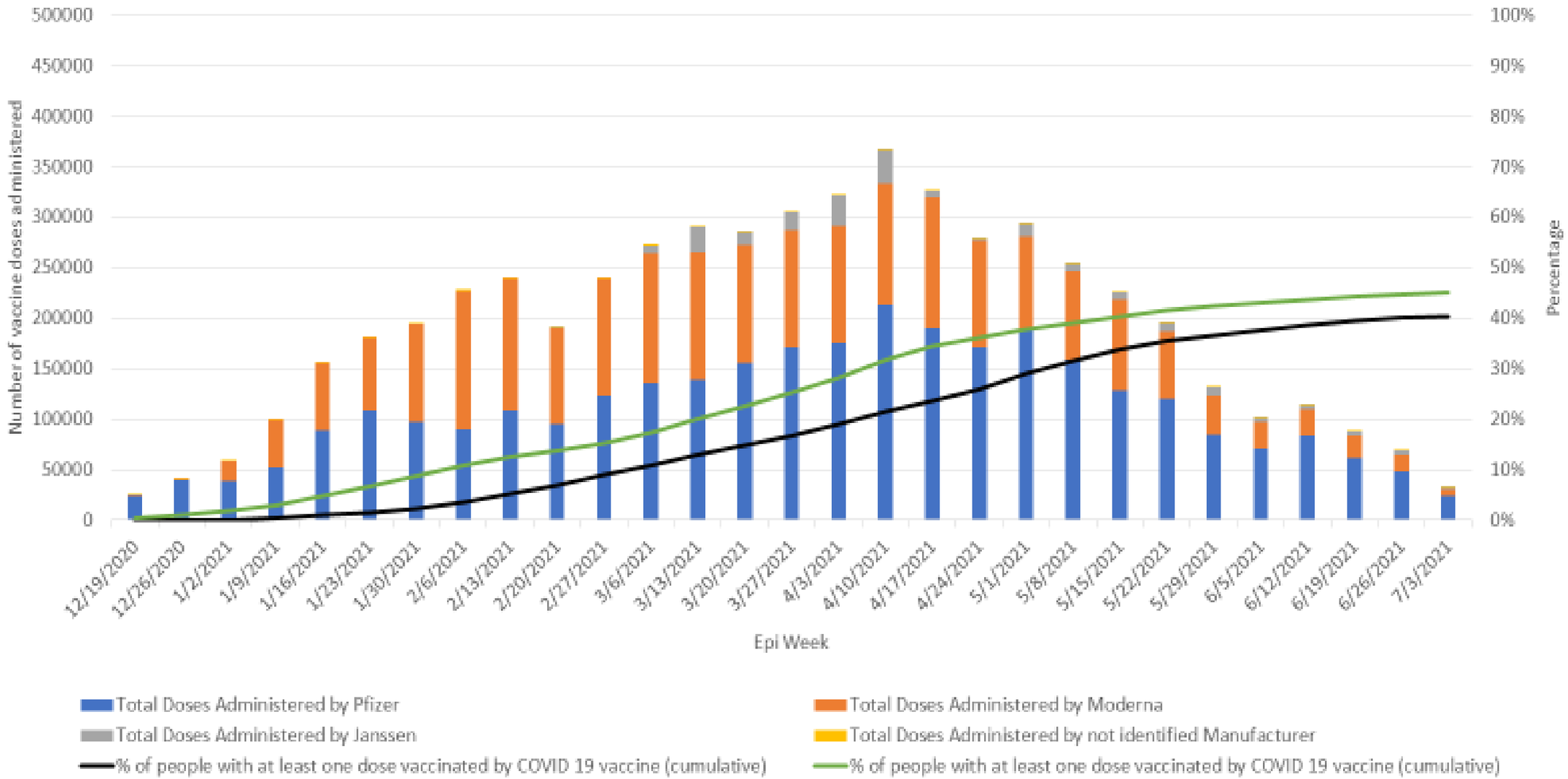
CDC, unpublished data, 2021. Data provided from the Routine Reporting and Data Visualization Team, Data Monitoring and Reporting Section, CDC Vaccine Task Force on July 2, 2021

Figure S17. Statewide Total Number of COVID-19 Vaccine Doses Administered and the Cumulative Percentage of People Fully and Partially Vaccinated by COVID-19 Vaccine, Oregon, December 19, 2020-July 2, 2021



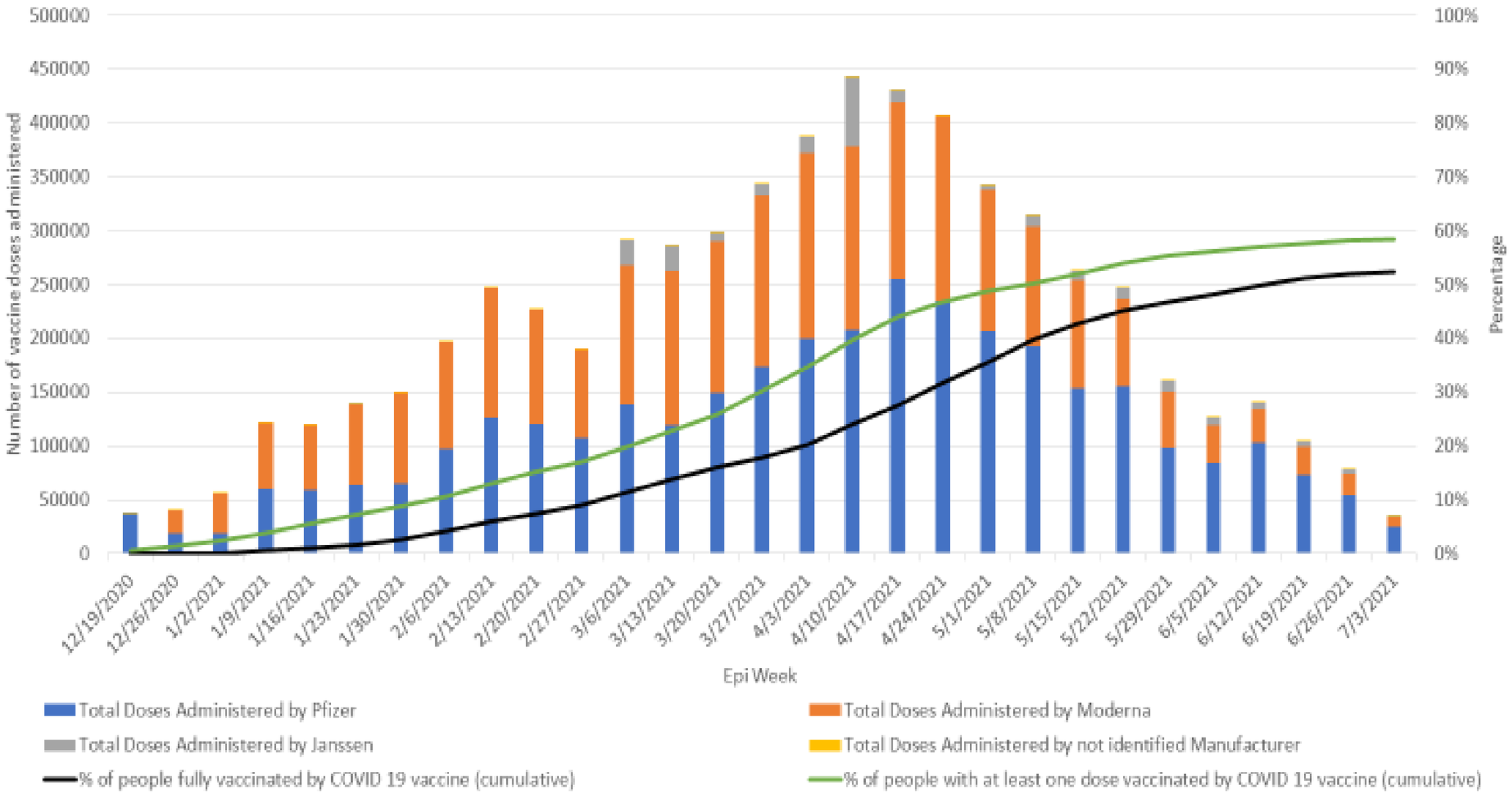
CDC, unpublished data, 2021. Data provided from the Routine Reporting and Data Visualization Team, Data Monitoring and Reporting Section, CDC Vaccine Task Force on July 2, 2021

Figure S18. Statewide Total Number of COVID-19 Vaccine Doses Administered and the Cumulative Percentage of People Fully and Partially Vaccinated by COVID-19 Vaccine, Indiana, December 19, 2020-July 2, 2021



CDC, unpublished data, 2021. Data provided from the Routine Reporting and Data Visualization Team, Data Monitoring and Reporting Section, CDC Vaccine Task Force on July 2, 2021

Figure S19. Statewide Total Number of COVID-19 Vaccine Doses Administered and the Cumulative Percentage of People Fully and Partially Vaccinated by COVID-19 Vaccine, Colorado, December 19, 2020-July 2, 2021



CDC, unpublished data, 2021. Data provided from the Routine Reporting and Data Visualization Team, Data Monitoring and Reporting Section, CDC Vaccine Task Force on July 2, 2021

D. Messenger RNA COVID-19 Vaccine Effectiveness among COVID-19-associated Hospitalizations

1. Variables included in inverse propensity to be vaccinated weights for Hospital VE

Variables unbalanced across COVID-19 infection status were considered potential confounders to include in the propensity-to-be-vaccinated weighting. Examining the association with COVID-19 infection status, the variables that had a standardized mean difference (SMD) of >0.1, and thus were included in the inverse-propensity-to-be-vaccinated weights, were site-region, age, race, ethnicity, type of admitting hospital, urban-rural classification of the facility, number of hospital beds, underlying conditions (including specific conditions), epidemiologic days, and 7-day moving average percent positivity (Table S22). Of these variables, site-region, type of admitting hospital, specific underlying conditions, and epidemiologic days were also unbalanced across vaccination status (SMD of >0.1 in bivariate associations with vaccination before inclusion in the propensity to be vaccinated weights).

The distribution of weights from each of the VE models for hospitalization is presented in Table S23. Across all models, outliers were at the extreme upper ends of the distributions. Therefore, weights were truncated at the 99.9 percentile for each model. Table S23 lists the relatively small number of medical events in each model that received the truncated weight.

After propensity-to-be-vaccinated weighting, all variables were balanced across the vaccinated and unvaccinated groups (all with SMD ≤0.02; Table S24). VE estimates derived from data balanced by inverse-propensity-to-be-vaccinated weights were similar to VE estimates before adjustment, with absolute differences generally <10%, with the exception of VE estimates

for the partial 1-dose vaccinations, which tended to have larger differences between VE estimates before and after adjustment (Table S16).

Table S22. Bivariate associations between covariates of interest and COVID-19 infection status for hospitalizations

	Sample		SARS-CoV-2 Negatives		SARS-CoV-2 Positives			
	N	Col. %	N	Row %	N	Row %	SMD[1]	Is variable included in Propensity Model[2]
A. Hospitalizations								
All hospitalizations	41552	100	37231	90	4321	10		
Site Characteristics								
Site-region							0.629	Yes
Columbia - site-region 1	3126	8	2458	79	668	21		
HealthPartners - site-region 1	973	2	916	94	57	6		
HealthPartners - site-region 2	16	0	12	75	4	25		
Intermountain Healthcare - site-region 1	248	1	219	88	29	12		
Intermountain Healthcare - site-region 2	238	1	204	86	34	14		
Intermountain Healthcare - site-region 3	1434	3	1253	87	181	13		
Intermountain Healthcare - site-region 4	721	2	630	87	91	13		
Intermountain Healthcare - site-region 5	67	0	58	87	9	13		
Intermountain Healthcare - site-region 6	479	1	411	86	68	14		
Intermountain Healthcare - site-region 7	74	0	61	82	13	18		
Intermountain Healthcare - site-region 8	649	2	517	80	132	20		
Kaiser Permanente Northern California - site-region 1	705	2	651	92	54	8		
Kaiser Permanente Northern California - site-region 2	510	1	453	89	57	11		
Kaiser Permanente Northern California - site-region 3	3200	8	2981	93	219	7		
Kaiser Permanente Northern California - site-region 4	5660	14	5478	97	182	3		
Kaiser Permanente Northern California - site-region 5	1660	4	1605	97	55	3		
Kaiser Permanente Northern California - site-region 6	676	2	663	98	13	2		
Kaiser Permanente Northern California - site-region 7	267	1	243	91	24	9		
Kaiser Permanente Northern California - site-region 8	1146	3	1085	95	61	5		
Kaiser Permanente Northwest - site-region 1	1376	3	1301	95	75	5		
Kaiser Permanente Northwest - site-region 2	394	1	362	92	32	8		
Kaiser Permanente Northwest - site-region 3	182	0	171	94	11	6		
Regenstrief Institute - site-region 1	2797	7	2386	85	411	15		
Regenstrief Institute - site-region 2	565	1	458	81	107	19		
Regenstrief Institute - site-region 3	170	0	122	72	48	28		
Regenstrief Institute - site-region 4	934	2	779	83	155	17		
Regenstrief Institute - site-region 5	3754	9	3334	89	420	11		
Regenstrief Institute - site-region 6	1151	3	991	86	160	14		

Regenstrief Institute - site-region 7	114	(	0	)	108	(	95	)	6	(	5	)
Regenstrief Institute - site-region 8	856	(	2	)	735	(	86	)	121	(	14	)
Regenstrief Institute - site-region 9	778	(	2	)	711	(	91	)	67	(	9	)
Regenstrief Institute - site-region 10	271	(	1	)	256	(	94	)	15	(	6	)
Regenstrief Institute - site-region missing	1047	(	3	)	896	(	86	)	151	(	14	)
University of Colorado - site-region 1	1585	(	4	)	1413	(	89	)	172	(	11	)
University of Colorado - site-region 2	1927	(	5	)	1719	(	89	)	208	(	11	)
University of Colorado - site-region 3	1802	(	4	)	1591	(	88	)	211	(	12	)
Patient Characteristics												
Sex											0.07	No
Male	19582	(	47	)	17418	(	89	)	2164	(	11	)
Female	21969	(	53	)	19812	(	90	)	2157	(	10	)
Race											0.29	Yes
White	29019	(	70	)	26357	(	91	)	2662	(	9	)
Black	3902	(	9	)	3414	(	87	)	488	(	13	)
Other[3]	2892	(	7	)	2692	(	93	)	200	(	7	)
Unknown	5739	(	14	)	4768	(	83	)	971	(	17	)
Ethnicity											0.23	Yes
Hispanic/Latinx Ethnicity	4574	(	11	)	3825	(	84	)	749	(	16	)
Not Hispanic/Latinx Ethnicity	31069	(	75	)	28190	(	91	)	2879	(	9	)
Unknown	5909	(	14	)	5216	(	88	)	693	(	12	)
Age, continuous (mean, std)	73.6	(	11	)	73.9	(	10.8	)	71	(	11.5	)	0.26	Yes
Setting Characteristics												
Admitting Hospital											0.25	Yes
Community	10633	(	26	)	9117	(	86	)	1516	(	14	)
Tertiary	29862	(	72	)	27208	(	91	)	2654	(	9	)
Unknown	1057	(	3	)	906	(	86	)	151	(	14	)
Urban-Rural Classification of Facility											0.2	Yes
Large Central Metro/Large Fringe Metro	26764	(	64	)	24228	(	91	)	2536	(	9	)
Medium Metro/Small Metro	12959	(	31	)	11508	(	89	)	1441	(	11	)
Micropolitan/Non-Core	733	(	2	)	544	(	74	)	189	(	26	)
Unknown	1106	(	3	)	951	(	86	)	155	(	14	)

Hospital Beds															0.14	No
0-49 beds	1238	(	3	)	1038	(	84	)	200	(	16	)				
50-99 beds	2595	(	6	)	2328	(	90	)	267	(	10	)				
100-249 beds	14629	(	35	)	13268	(	91	)	1361	(	9	)				
250+ beds	22033	(	53	)	19691	(	89	)	2342	(	11	)				
Unknown	1057	(	3	)	906	(	86	)	151	(	14	)				
Hospital Ownership															0.05	No
Non-Profit	39859	(	96	)	35751	(	90	)	4108	(	10	)				
For Profit / Other	1693	(	4	)	1480	(	87	)	213	(	13	)				
Underlying medical conditions (more than one may apply)																
Chronic respiratory condition	27423	(	66	)	24689	(	90	)	2734	(	10	)			0.07	No
Chronic non-respiratory condition	37899	(	91	)	34289	(	90	)	3610	(	10	)			0.26	Yes
Asthma	6277	(	15	)	5907	(	94	)	370	(	6	)			0.22	Yes
COPD	12645	(	30	)	12035	(	95	)	610	(	5	)			0.44	Yes
Other Chronic Lung Disease	17624	(	42	)	15196	(	86	)	2428	(	14	)			0.31	Yes
Heart Failure	12862	(	31	)	12126	(	94	)	736	(	6	)			0.37	Yes
Ischemic Heart Disease	13134	(	32	)	12142	(	92	)	992	(	8	)			0.22	Yes
Hypertension	27382	(	66	)	24908	(	91	)	2474	(	9	)			0.2	Yes
Other Heart Disease	22266	(	54	)	20595	(	92	)	1671	(	8	)			0.34	Yes
Stroke	1850	(	4	)	1700	(	92	)	150	(	8	)			0.06	No
Other Cerebrovascular Disease	1978	(	5	)	1836	(	93	)	142	(	7	)			0.08	No
Diabetes Type 1	244	(	1	)	225	(	92	)	19	(	8	)			0.02	No
Diabetes Type 2	14106	(	34	)	12603	(	89	)	1503	(	11	)			0.02	No
Diabetes due to underlying conditions or other specified diabetes	211	(	1	)	164	(	78	)	47	(	22	)			0.07	No
Other Metabolic Disease (excluding diabetes)	26286	(	63	)	24006	(	91	)	2280	(	9	)			0.24	Yes
Clinical Obesity	9422	(	23	)	8385	(	89	)	1037	(	11	)			0.04	No
Clinical Underweight	4601	(	11	)	4118	(	90	)	483	(	10	)			0.004	No
Renal Disease	13666	(	33	)	12614	(	92	)	1052	(	8	)			0.21	Yes
Liver Disease	4025	(	10	)	3714	(	92	)	311	(	8	)			0.1	No
Blood Disorder	3226	(	8	)	2928	(	91	)	298	(	9	)			0.04	No
Immunosuppression	15726	(	38	)	14468	(	92	)	1258	(	8	)			0.21	Yes
Organ Transplant	612	(	1	)	553	(	90	)	59	(	10	)			0.01	No
Cancer	5997	(	14	)	5686	(	95	)	311	(	5	)			0.26	Yes
Dementia	4397	(	11	)	3963	(	90	)	434	(	10	)			0.02	No
Other Neurological/Musculoskeletal Disorder	13787	(	33	)	12737	(	92	)	1050	(	8	)			0.22	Yes

Down Syndrome	13	(	0	)	13	(	100	)	0	(	0	)	0.03	No
Time Considerations (Median, Q1-Q3)														
Epi-curve (days)	4/17	(	3/23-5/12	)	4/18	(	3/24-5/12	)	4/12	(	3/15-5/10	)	0.182	Yes
7-day Moving Average Percent Positivity (days)	4.2	(	2.1-5.9	)	4	(	2.0-5.7	)	5.5	(	4.0-7.3	)	0.55	Yes

[1]Illustrates SMD prior to propensity weighting, to show differences between SARS-CoV-2 negative and positive groups.

[2]Variables with a SMD > 0.1 were included in PS weighting.

[3]Other race include Asian, Hawaiian or Other Pacific islander, American Indian or Alaskan Native, Other not-listed and multi-race.

Table S23. Quantiles of Weights used for VE Estimates among COVID-19-associated hospitalizations and intensive care unit (ICU) admissions events

	50%	Min	Max	1%	25%	75%	99%	100%	Number Truncated
mRNA VE among COVID-19 ED/UC medical events									
VE both mRNA vaccines (aged ≥50 years)	1.53	1.01	43.83	1.06	1.27	2.16	6.59	11.02	41
By vaccine product among COVID-19 medical events									
VE of BioNTech-Pfizer mRNA (aged ≥50 years)	1.05	1.00	146.78	1.01	1.03	1.11	19.73	43.08	12
VE of Moderna mRNA (aged ≥50 years)	1.46	1.01	30.37	1.03	1.19	2.00	7.67	15.22	30
Ad26.COV2.S (Johnson & Johnson)	1.05	1.00	146.78	1.01	1.03	1.11	19.73	43.08	12
By Age Group among COVID-19 medical events									
VE both mRNA vaccines (aged 50-64 years)	1.53	1.04	12.94	1.08	1.28	2.11	6.15	9.37	9
VE both mRNA vaccines (aged 65-74 years)	1.57	1.01	34.46	1.03	1.29	2.13	6.03	10.53	13
VE both mRNA vaccines (aged 75-84 years)	1.50	1.01	15.98	1.06	1.24	2.09	7.15	11.74	13
VE both mRNA vaccines (aged ≥85 years)	1.45	1.01	14.55	1.06	1.24	2.07	6.67	10.07	8
By Race and Ethnicity among COVID-19 medical events									
VE both mRNA vaccines among White adults aged ≥50 years	1.56	1.02	19.69	1.07	1.28	2.14	6.63	11.21	29
VE both mRNA vaccines among Black adults aged ≥50 years	1.47	1.03	15.40	1.05	1.26	2.01	5.83	11.03	4
VE both mRNA vaccines among Other or Unknown aged ≥50 years	1.30	1.01	12.00	1.04	1.18	1.76	8.24	11.04	3
VE both mRNA vaccines among Hispanic adults aged ≥50 years	1.47	1.01	12.45	1.07	1.26	2.06	5.90	7.98	5
VE both mRNA vaccines among Non-Hispanic adults aged ≥50 years	1.51	1.02	23.05	1.06	1.25	2.14	6.71	10.72	31
By Presence of Absence of Underlying Chronic Medical Conditions Associated with Increased Risk of Severe Respiratory Disease									
VE both mRNA vaccines among aged ≥50 years with no chronic condition	1.60	1.02	12.67	1.04	1.32	2.13	5.11	9.69	3
VE both mRNA vaccines among aged ≥50 years with ≥1 chronic respiratory condition	1.50	1.01	40.26	1.05	1.25	2.11	6.90	11.25	27
VE both mRNA vaccines among aged ≥50 years with ≥1 chronic non-respiratory condition	1.52	1.01	44.36	1.06	1.27	2.14	6.75	11.17	38
By Alternative Clinical Outcomes									

VE both mRNA vaccines among aged ≥50 years with acute respiratory illness diagnosis	1.51	1.01	36.77	1.05	1.26	2.13	6.82	11.31	30
VE both mRNA vaccines among aged ≥50 years with clinical pneumonia diagnosis	1.54	1.00	24.53	1.05	1.28	2.14	5.91	9.53	10
VE both mRNA vaccines among aged ≥50 years with CLI/signs and symptoms as primary discharge code	1.56	1.01	31.35	1.05	1.30	2.14	6.04	10.02	25
ICU admission	1.49	1.02	19.63	1.06	1.25	2.08	6.13	8.99	8

Table S24. Unweighted and weighted standardized mean differences (SMD) for variables included in PS model for mRNA-specific VE estimates - Hospitalizations events

	Sample	Unvaccinated		Partially or Fully Vaccinated		Unweighted	Weighted
	N	N	(Row %)	N	(Row %)	SMD[2]	SMD[3]
A. Hospitalizations							
All hospitalizations	36554	16711	(46)	19843	(54)	-	-
Site Characteristics							
Site-region							
Columbia - site-region 1	2421	1586	(66)	835	(34)	-0.212	-0.002
HealthPartners - site-region 1	908	337	(37)	571	(63)	0.055	0.004
HealthPartners - site-region 2	12	5	(42)	7	(58)	0.003	0.002
Intermountain Healthcare - site-region 1	211	107	(51)	104	(49)	-0.015	-0.005
Intermountain Healthcare - site-region 2	200	71	(36)	129	(65)	0.031	0.003
Intermountain Healthcare - site-region 3	1227	508	(41)	719	(59)	0.032	0.003
Intermountain Healthcare - site-region 4	624	265	(42)	359	(58)	0.017	0
Intermountain Healthcare - site-region 5	57	26	(46)	31	(54)	0	0.001
Intermountain Healthcare - site-region 6	399	189	(47)	210	(53)	-0.007	0
Intermountain Healthcare - site-region 7	60	26	(43)	34	(57)	0.004	0
Intermountain Healthcare - site-region 8	492	254	(52)	238	(48)	-0.028	-0.009
Kaiser Permanente Northern California - site-region 1	634	188	(30)	446	(70)	0.086	0.002
Kaiser Permanente Northern California - site-region 2	445	165	(37)	280	(63)	0.039	0.002
Kaiser Permanente Northern California - site-region 3	2921	823	(28)	2098	(72)	0.208	0.006
Kaiser Permanente Northern California - site-region 4	5296	1135	(21)	4161	(79)	0.403	0.018
Kaiser Permanente Northern California - site-region 5	1542	303	(20)	1239	(80)	0.22	0.016
Kaiser Permanente Northern California - site-region 6	642	115	(18)	527	(82)	0.15	0.012
Kaiser Permanente Northern California - site-region 7	239	75	(31)	164	(69)	0.047	0.002
Kaiser Permanente Northern California - site-region 8	1060	267	(25)	793	(75)	0.143	0.008
Kaiser Permanente Northwest - site-region 1	2356	1596	(68)	760	(32)	-0.233	-0.012
Kaiser Permanente Northwest - site-region 2	452	230	(51)	222	(49)	-0.023	-0.001
Kaiser Permanente Northwest - site-region 3	122	73	(60)	49	(40)	-0.033	-0.005
Regenstrief Institute - site-region 1	771	438	(57)	333	(43)	-0.066	-0.008
Regenstrief Institute - site-region 2	3294	1815	(55)	1479	(45)	-0.119	-0.008
Regenstrief Institute - site-region 3	984	548	(56)	436	(44)	-0.067	-0.004
Regenstrief Institute - site-region 4	106	58	(55)	48	(45)	-0.02	-0.003
Regenstrief Institute - site-region 5	733	411	(56)	322	(44)	-0.06	-0.006
Regenstrief Institute - site-region 6	698	320	(46)	378	(54)	-0.001	0.001

Regenstrief Institute - site-region 7	254	129	(	51	)	125	(	49	)	-0.017	0
Regenstrief Institute - site-region 8	888	538	(	61	)	350	(	39	)	-0.095	-0.004
Regenstrief Institute - site-region 9	1413	996	(	70	)	417	(	30	)	-0.2	-0.01
Regenstrief Institute - site-region 10	1719	1043	(	61	)	676	(	39	)	-0.134	-0.006
Regenstrief Institute - site-region missing	1591	1263	(	79	)	328	(	21	)	-0.289	-0.014
University of Colorado - site-region 1	1256	560	(	45	)	696	(	55	)	0.009	0.001
University of Colorado - site-region 2	357	179	(	50	)	178	(	50	)	-0.018	0.001
University of Colorado - site-region 3	170	69	(	41	)	101	(	59	)	0.014	0.002
Patient Characteristics											
Sex											
Female	19444	8866	(	46	)	10578	(	54	)	-	-
Male	17110	7845	(	46	)	9265	(	54	)	-	-
Race											
White	25923	11631	(	45	)	14292	(	55	)	0.053	0.007
Black	3333	1957	(	59	)	1376	(	41	)	-0.166	-0.012
Other[4]	2616	755	(	29	)	1861	(	71	)	0.189	0.011
Unknown	4682	2368	(	51	)	2314	(	49	)	-0.075	-0.008
Ethnicity											
Hispanic/Latinx Ethnicity	27749	12901	(	46	)	14848	(	54	)	-0.055	-0.008
Not Hispanic/Latinx Ethnicity	3744	1720	(	46	)	2024	(	54	)	-0.003	0.006
Unknown	5061	2090	(	41	)	2971	(	59	)	0.071	0.005
Age, continuous (mean, std)	73.99	72.05	(	11	)	75.62	(	10	)	0.33	0.02
Setting Characteristics											
Admitting Hospital											
Community	8933	4606	(	52	)	4327	(	48	)	-0.134	-0.014
Tertiary	26723	11559	(	43	)	15164	(	57	)	0.164	0.015
Unknown	898	546	(	61	)	352	(	39	)	-0.096	-0.006
Urban-Rural Classification of Facility											
Large Central Metro/Large Fringe Metro	23723	10219	(	43	)	13504	(	57	)	0.145	0.005
Medium Metro/Small Metro	11354	5647	(	50	)	5707	(	50	)	-0.109	-0.002
Micropolitan/Non-Core	536	282	(	53	)	254	(	47	)	-0.034	-0.007
Unknown	941	563	(	60	)	378	(	40	)	-0.092	-0.003

Hospital Beds										
0-49 beds	1015	449	(	44	)	566	(	56	)	0.01	-0.01
50-99 beds	2287	902	(	39	)	1385	(	61	)	0.065	-0.002
100-249 beds	12932	4816	(	37	)	8116	(	63	)	0.253	0.008
250+ beds	19422	9998	(	51	)	9424	(	49	)	-0.247	-0.001
Unknown	898	546	(	61	)	352	(	39	)	-0.096	-0.006
Hospital Ownership										
Non-Profit	35089	15869	(	45	)	19220	(	55	)	-	-
For Profit / Other	1465	842	(	57	)	623	(	43	)	-	-
Underlying medical conditions (more than one may apply)										
Chronic respiratory condition	24229	10659	(	44	)	13570	(	56	)	-	-
Chronic non-respiratory condition	33644	15046	(	45	)	18598	(	55	)	0.136	0.003
Asthma	5773	1986	(	34	)	3787	(	66	)	0.197	0.018
COPD	11821	5667	(	48	)	6154	(	52	)	-0.062	-0.005
Other Chronic Lung Disease	14908	6910	(	46	)	7998	(	54	)	-0.021	-0.009
Heart Failure	11871	5198	(	44	)	6673	(	56	)	0.054	0.003
Ischemic Heart Disease	11952	5035	(	42	)	6917	(	58	)	0.101	0.006
Hypertension	24447	10403	(	43	)	14044	(	57	)	0.181	0.014
Other Heart Disease	20204	8645	(	43	)	11559	(	57	)	0.131	0.012
Stroke	1673	859	(	51	)	814	(	49	)	-	-
Other Cerebrovascular Disease	1790	846	(	47	)	944	(	53	)	-	-
Diabetes Type 1	215	93	(	43	)	122	(	57	)	-	-
Diabetes Type 2	12332	5336	(	43	)	6996	(	57	)	-	-
Diabetes due to underlying conditions or other specified diabetes	164	93	(	57	)	71	(	43	)	-	-
Other Metabolic Disease (excluding diabetes)	23541	9766	(	41	)	13775	(	59	)	0.229	0.015
Clinical Obesity	8190	3697	(	45	)	4493	(	55	)	-	-
Clinical Underweight	4031	2189	(	54	)	1842	(	46	)	-	-
Renal Disease	12353	4896	(	40	)	7457	(	60	)	0.175	0.017
Liver Disease	3629	1709	(	47	)	1920	(	53	)	-	-
Blood Disorder	2864	1242	(	43	)	1622	(	57	)	-	-
Immunosuppression	14207	6137	(	43	)	8070	(	57	)	0.081	0.007
Organ Transplant	541	236	(	44	)	305	(	56	)	-	-
Cancer	5586	2428	(	43	)	3158	(	57	)	0.039	0.008
Dementia	3880	1774	(	46	)	2106	(	54	)	-	-
Other Neurological/Musculoskeletal Disorder	12490	5720	(	46	)	6770	(	54	)	-0.002	0

Down Syndrome	13	9	(	69	)	4	(	31	)	-	-
Time Considerations (Median, Q1-Q3)										
Epi-curve (days)	4/18	4/08	(	3/11-5/06	)	4/25	(	3/31-5/17	)	0.462	0.045
7-day Moving Average Percent Positivity (days)	3.99	4.94	(	3.2-6.4	)	3.14	(	1.3-5.1	)	-0.571	-0.041

[1]Variables with a SMD > 0.1 were included in PS weighting.

[2]Illustrates SMD prior to propensity weighting, to show differences between vaccinated and unvaccinated groups.

[3]SMD values after propensity weighting, SMD < 0.1 indicates no differences between groups, and that balance was achieved.

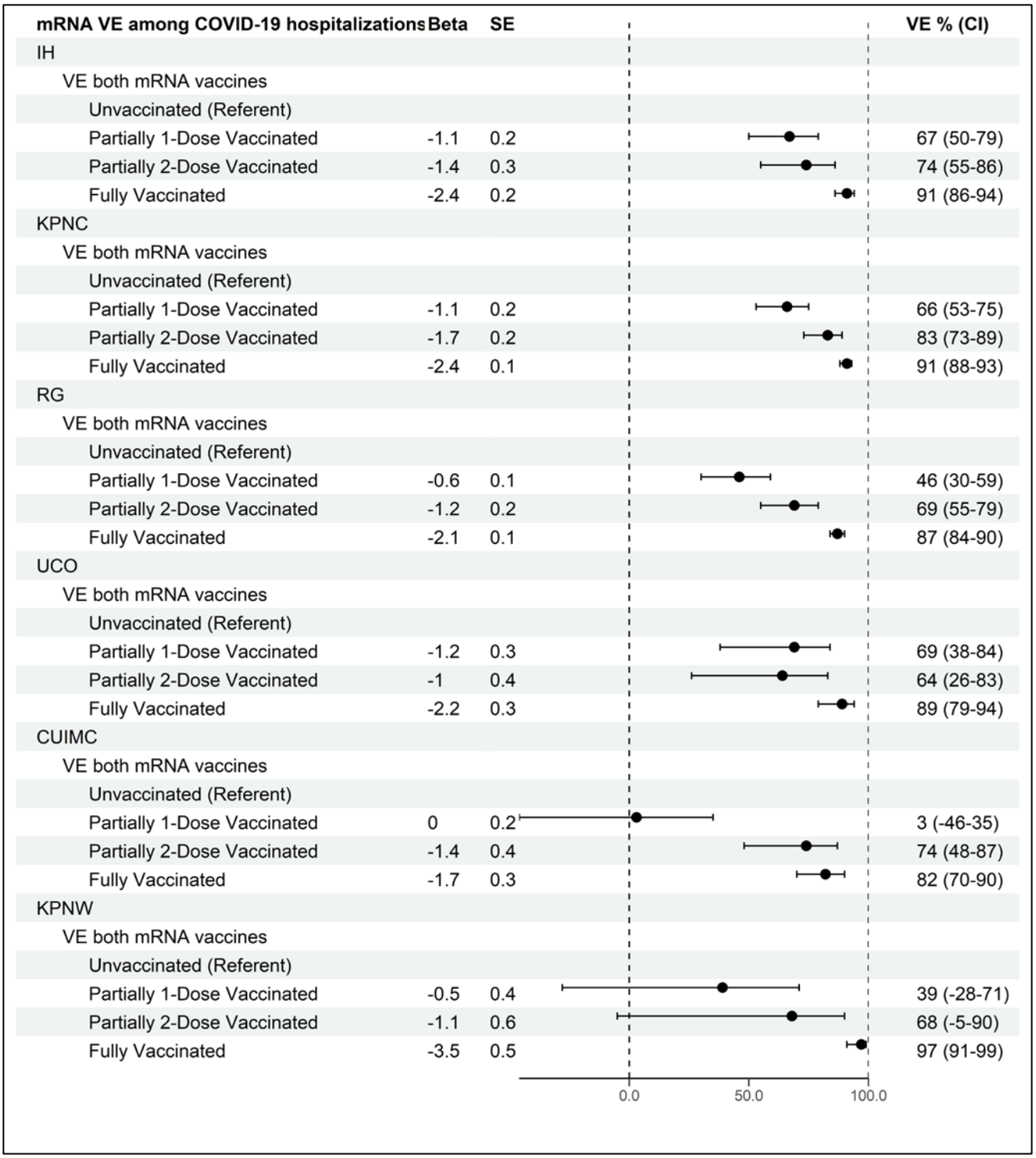
[4]Other race include Asian, Hawaiian or Other Pacific islander, American Indian or Alaskan Native, Other not-listed and multi-race.

2. Hospital VE Sensitivity Analysis: Between Partner Heterogeneity

In a sensitivity analysis examining potential heterogeneity in the VE estimates across partners, the mRNA VE estimates among COVID-19 hospitalizations were similar (range=82%-97% for full vaccination, and 64%-83% for partial 2-dose vaccination). Greater variability was observed across partners in the VE estimates for partial 1-dose vaccination (range=3%-69%) (Table S17).

In exploratory examinations of results heterogeneity, we examined estimates of VE across six Network partners for full mRNA vaccination and partial-1-dose mRNA vaccination against COVID-19 associated hospitalization (Figure S20). A stratified model for HealthPartners was not calculated because of relatively small sample size which was not adequate for propensity score calculation. For full mRNA vaccination, the Cochran's χ^2 (or Q-test) (Q [5]=9.2, p=0.10) did not reject the null hypothesis of homogeneity in VE across Network partners. The I^2 index also indicated minimal heterogeneity in results (I^2=15.2%), using standard thresholds. In contrast, for partial-1-dose mRNA vaccination, both the Cochran's χ^2 (or Q-test) and I^2 index indicated substantial heterogeneity in VE estimates across Network partners (Q[5]=7.5, p=0.19; I^2=34.6%).

Figure S20. Messenger RNA (mRNA) vaccine effectiveness (VE) against COVID-19-associated hospitalizations by study site, with statistics assessing heterogeneity



Abbreviations: Standard error = SE

For partial-1-dose vaccination, I2 = 34.6%, Q = 7.5, p=0.19 (df=5)

For full vaccination, I2 = 15.2%, Q = 9.2, p=0.10 (df=5)

3. Hospital VE Sensitivity Analysis: Alternative Clinical Outcomes

In a sensitivity analysis to explore possible heterogeneity in VE by alternative clinical outcome, the mRNA VE among hospitalization with a clinical pneumonia diagnosis was 92% (95%CI=90%-94%) for full vaccination, 80% (95%CI=71%-86%) for partial 2-dose vaccination, and 49% (95%CI=36%-60%) for partial 1-dose vaccination. The mRNA VE among hospitalization with CLI as the primary discharge code was 88% (95%CI=86%-91%) for full vaccination, 68% (95%CI=57%-77%) for partial 2-dose vaccination, and 45% (95%CI=33%-56%) for partial 1-dose vaccination (Table S16). The mRNA VE estimates for both of these alternative outcomes were similar and had overlapping confidence intervals relative to the main mRNA VE estimate among COVID-19 hospitalizations.

4. Hospital VE Sensitivity Analysis: Exclude Historical SARS-CoV-2 Positives

In a sensitivity analysis excluding patients with any SARS-CoV-2 positive result from molecular or antigen assays >14 days prior to the index date, the mRNA VE among COVID-19 hospitalization was 90% (95%CI=88%-92%) for full vaccination, 73% (95%CI=64%-80%) for partial 2-dose vaccination, and 53% (95%CI=44%-61%) for partial 1-dose vaccination (Table S25). These estimates were very similar to VE estimates in the main analysis (differences of ≤1% points).

Table S25. messenger RNA (mRNA) vaccine effectiveness (VE) among COVID-19-associated hospitalizations, intensive care unit (ICU) admissions, and emergency department and urgent care (ED/UC) medical events among those without historical positives

	Total	SARS-CoV-2 Positive[1]	(Row %)	VE[2] % (95% CI)
mRNA VE among COVID-19 hospitalizations				
VE both mRNA vaccines				
Unvaccinated (Referent)	15755	3039	(19.3)	
Partially 1-Dose Vaccinated	1895	167	(8.8)	53 (44 - 61)
Partially 2-Dose Vaccinated	1378	70	(5.1)	73 (64 - 80)
Fully Vaccinated	6549	135	(2.1)	90 (88 - 92)
VE of BioNTech-Pfizer mRNA				
Unvaccinated (Referent)	15755	3039	(19.3)	
Partially 1-Dose Vaccinated	919	107	(11.6)	25 (5 - 41)
Partially 2-Dose Vaccinated	777	42	(5.4)	71 (58 - 81)
Fully Vaccinated	3645	87	(2.4)	88 (84 - 90)
VE of Moderna mRNA				
Unvaccinated (Referent)	15755	3039	(19.3)	
Partially 1-Dose Vaccinated	976	60	(6.1)	70 (60 - 78)
Partially 2-Dose Vaccinated	601	28	(4.7)	73 (58 - 83)
Fully Vaccinated	2904	48	(1.7)	93 (90 - 95)
mRNA VE among COVID-19 ICU admission				
VE both mRNA vaccines				
Unvaccinated (Referent)	3181	592	(18.6)	
Partially 1-Dose Vaccinated	286	23	(8)	50 (17 - 70)
Partially 2-Dose Vaccinated	208	12	(5.8)	73 (48 - 86)
Fully Vaccinated	1018	23	(2.3)	90 (84 - 94)
mRNA VE among COVID-19 ED/UC				
VE both mRNA vaccines				
Unvaccinated (Referent)	11134	2752	(24.7)	
Partially 1-Dose Vaccinated	1794	145	(8.1)	68 (61 - 74)

Partially 2-Dose Vaccinated	1201	56	(	4.7	)	83	(	77	-	87	)
Fully Vaccinated	5731	136	(	2.4	)	92	(	90	-	93	)
VE of BioNTech-Pfizer mRNA											
Unvaccinated (Referent)	11134	2752	(	24.7	)						
Partially 1-Dose Vaccinated	864	84	(	9.7	)	59	(	46	-	69	)
Partially 2-Dose Vaccinated	676	27	(	4	)	85	(	77	-	90	)
Fully Vaccinated	3441	94	(	2.7	)	90	(	86	-	92	)
VE of Moderna mRNA											
Unvaccinated (Referent)	11134	2752	(	24.7	)						
Partially 1-Dose Vaccinated	930	61	(	6.6	)	74	(	65	-	81	)
Partially 2-Dose Vaccinated	525	29	(	5.5	)	77	(	64	-	85	)
Fully Vaccinated	2290	42	(	1.8	)	93	(	90	-	95	)

[1]SARS-CoV-2 infection confirmed by molecular assays.

[2]Adjusted model using inverse propensity weights, calculated using strata specific data, in regression doubly accounting for calendar time and daily virus circulation.

5. Hospital VE Sensitivity Analysis: Propensity of Clinical Testing for SARS-CoV-2

In a sensitivity analysis to examine potential bias introduced by clinician-ordered testing, inverse propensity weights (IPW) were calculated to account for both propensity to be vaccinated and propensity to be tested. The model for propensity for vaccination was build using only those who tested negative for SARS-CoV-2, while the model for propensity for testing was built with all the data. Among 38,130 CLI hospitalizations across the five partners contributing to this sensitivity analysis (HP, IH, KPNW, RG, and UCO), 25,663 (67%) had available test results for SARS-CoV-2 (Table S26). Among hospitalizations, testing percentage varied by site, ranging from 59% within IM to 95% within HP. Higher testing percentages were observed for encounters at tertiary hospitals (72%) or those in settings classified as large central metro/large fringe metro areas (74%), as well as among patients who were of other race (80%), Hispanic (77%), or unvaccinated (71% compared to 63% who received any COVID-19 vaccine).

The proportion of vaccination varied by partner, age, race, and ethnicity, and this variation was similar among both those tested and those not tested for SARS-CoV-2 (Table_2; Table S27).

The mRNA VE estimates among COVID-19 hospitalization accounting for testing and vaccination when excluding KPNC and CUIMC were 88% (95%CI=85%-90%) for full vaccination, 75% (95%CI=66%-81%) for partial 2-dose vaccination, and 59% (95%CI=48%-67%) for partial 1-dose vaccination (Table S28). In comparison, the mRNA VE estimates in the main analysis that accounted only for the propensity to be vaccinated were 89% (95%CI=87%-91%) for full vaccination, 73% (95%CI=66%-79%) for partial 2-dose vaccination, and 54% (95%CI=47%-61%) for partial 1-dose vaccination (Table S16).

Table S26. Characteristics of adults with medically attended COVID-19-like illness and the percent with SARS-CoV-2 testing within 14 days prior to, or within <72 hours after, the time of hospital admission or emergency department or urgent care visit

	Total Medical Events N (Col. %)	**Tested for SARS-CoV-2** N (Row %)	**Not Tested for SARS-CoV-2** N (Row %)	**SMD**
A. Hospitalizations				
All hospitalizations	38130 (100)	25663 (67)	12467 (33)	
Sites				0.75
HealthPartners	1046 (3)	989 (95)	57 (5)	
Intermountain Healthcare	6611 (17)	3910 (59)	2701 (41)	
Kaiser Permanente Northwest	2107 (6)	1953 (93)	154 (7)	
Regenstrief Institute	22597 (59)	13496 (60)	9101 (40)	
University of Colorado	5769 (15)	5315 (92)	454 (8)	
Age groups				0.04
50-64 years	9168 (24)	6113 (67)	3055 (33)	
65-74 years	12076 (32)	8204 (68)	3872 (32)	
75-84 years	10918 (29)	7306 (67)	3612 (33)	
≥85 years	5968 (16)	4040 (68)	1928 (32)	
Sex				0.02
Male	18111 (47)	12268 (68)	5843 (32)	
Female	20018 (52)	13394 (67)	6624 (33)	
Other/unknown	1 (0)	1 (100)	0 (0)	
Race (regardless of ethnicity)				0.24
White	29615 (78)	19982 (67)	9633 (33)	
Black	2488 (7)	1933 (78)	555 (22)	
Other[1]	803 (2)	641 (80)	162 (20)	
Unknown	5224 (14)	3107 (59)	2117 (41)	
Ethnicity (regardless of race)				0.20
Hispanic	1394 (4)	1080 (77)	314 (23)	
Non-Hispanic	31561 (83)	21698 (69)	9863 (31)	
Unknown	5175 (14)	2885 (56)	2290 (44)	
Admitting Hospital Type				0.28

Community	14108 (37)	8878 (63)	5230 (37)
Tertiary	21672 (57)	15568 (72)	6104 (28)
Unknown	2350 (6)	1217 (52)	1133 (48)
Urban-Rural Classification of Facility			0.37
Large Central Metro/Large Fringe Metro	18036 (47)	13270 (74)	4766 (26)
Medium Metro/Small Metro	15315 (40)	10127 (66)	5188 (34)
Micropolitan/Non-Core	2372 (6)	1000 (42)	1372 (58)
Unknown	2407 (6)	1266 (53)	1141 (47)
Underlying respiratory condition at discharge			0.18
Chronic respiratory condition[2]	21671 (57)	15317 (71)	6354 (29)
None	16459 (43)	10346 (63)	6113 (37)
Underlying non-respiratory condition at discharge			0.11
Chronic non-respiratory condition[3]	32348 (85)	22118 (68)	10230 (32)
None	5782 (15)	3545 (61)	2237 (39)
COVID-19-like illness (CLI) ICD discharge codes			0.24
≥1 CLI clinical diagnosis code[4]	24480 (64)	17431 (71)	7049 (29)
No clinical diagnosis but ≥1 CLI sign or symptom[5]	13650 (36)	8232 (60)	5418 (40)
CLI diagnosis and placement among discharge codes			0.00
CLI is first or primary diagnosis	12913 (34)	8699 (67)	4214 (33)
CLI is not first or primary diagnosis	25217 (66)	16964 (67)	8253 (33)
Intensive care unit (ICU) admissions			0.17
Admitted to ICU	6128 (16)	4644 (76)	1484 (24)
Not in ICU during hospitalization	32002 (84)	21019 (66)	10983 (34)
COVID-19 Vaccinations			0.20
Unvaccinated	21639 (57)	15299 (71)	6340 (29)
BNT162b2 (Pfizer-BioNTech)	7865 (21)	5143 (65)	2722 (35)
mRNA-1273 (Moderna)	8151 (21)	4933 (61)	3218 (39)
Ad26.COV2.S (Johnson & Johnson)	475 (1)	288 (61)	187 (39)
B. Emergency Department (ED) and Urgent Care (UC) Visits			

All ED and UC Visits	71866 (100)	22321 (31)	49545 (69)	
-	-	-	-	-
By medical event setting				-0.11
ED visits	59616 (83)	19154 (32)	40462 (68)	
UC visits	12250 (17)	3167 (26)	9083 (74)	
Sites				0.19
Intermountain Healthcare	29466 (41)	9008 (31)	20458 (69)	
Kaiser Permanente Northwest	11441 (16)	4712 (41)	6729 (59)	
Regenstrief Institute	30959 (43)	8601 (28)	22358 (72)	
Age groups				0.10
50-64 years	26589 (37)	7674 (29)	18915 (71)	
65-74 years	21715 (30)	6802 (31)	14913 (69)	
75-84 years	16192 (23)	5400 (33)	10792 (67)	
≥85 years	7370 (10)	2445 (33)	4925 (67)	
Sex				0.10
Male	30090 (42)	10106 (34)	19984 (66)	
Female	41772 (58)	12214 (29)	29558 (71)	
Other/unknown	4 (0)	1 (25)	3 (75)	
Race (regardless of ethnicity)				0.11
White	57192 (80)	17999 (31)	39193 (69)	
Black	2758 (4)	869 (32)	1889 (68)	
Other[1]	1965 (3)	744 (38)	1221 (62)	
Unknown	9951 (14)	2709 (27)	7242 (73)	
Ethnicity (regardless of race)				0.09
Hispanic	3749 (5)	1184 (32)	2565 (68)	
Non-Hispanic	57984 (81)	18462 (32)	39522 (68)	
Unknown	10133 (14)	2675 (26)	7458 (74)	
Urban-Rural Classification of Facility				0.14
Large Central Metro/Large Fringe Metro	28458 (40)	9580 (34)	18878 (66)	
Medium Metro/Small Metro	29066 (40)	8925 (31)	20141 (69)	
Micropolitan/Non-Core	9943 (14)	2526 (25)	7417 (75)	
Unknown	4399 (6)	1290 (29)	3109 (71)	

Underlying respiratory condition at discharge				0.28
Chronic respiratory condition[2]	18577 (26)	7678 (41)	10899 (59)	
None	53289 (74)	14643 (27)	38646 (73)	
Underlying non-respiratory condition at discharge				0.24
Chronic non-respiratory condition[3]	36403 (51)	13139 (36)	23264 (64)	
None	35463 (49)	9182 (26)	26281 (74)	
COVID-19-like illness (CLI) ICD discharge codes				0.45
≥1 CLI clinical diagnosis code[4]	28121 (39)	12107 (43)	16014 (57)	
No clinical diagnosis but ≥1 CLI sign or symptom[5]	43745 (61)	10214 (23)	33531 (77)	
CLI diagnosis and placement among discharge codes				0.03
CLI is first or primary diagnosis	37144 (52)	11760 (32)	25384 (68)	
CLI is not first or primary diagnosis	34722 (48)	10561 (30)	24161 (70)	
COVID-19 Vaccinations				0.24
Unvaccinated	34351 (48)	12316 (36)	22035 (64)	
BNT162b2 (Pfizer-BioNTech)	19295 (27)	5347 (28)	13948 (72)	
mRNA-1273 (Moderna)	16312 (23)	4194 (26)	12118 (74)	
Ad26.COV2.S (Johnson & Johnson)	1907 (3)	464 (24)	1443 (76)	

Note: All patients with indeterminate immunization status (receipt of dose-1 of mRNA vaccine or J&J vaccine 1-13 days prior to index test date) were excluded from this table. Patients with SARS-CoV-2 testing, but only indeterminate or unknown result(s), are considered tested for the purpose of this table.

Abbreviations: Standard Mean Difference (SMD), COVID-like Illness (CLI), International Classification of Disease (ICD), Intensive Care Unit (ICU), Emergency Department (ED), Urgent Care (UC)

[1]Other race include: Asian, Hawaiian or Other Pacific islander, American Indian or Alaskan Native, Other not-listed and multi-race.

[2]Underlying chronic respiratory conditions include: asthma, chronic obstructive pulmonary disease (COPD), other lung disease.

[3]Underlying chronic non-respiratory conditions include: heart failure, ischemic heart disease, hypertension, other heart disease, stroke, other cerebrovascular disease, diabetes (type 1, 2 and due to other specified conditions), other metabolic disease, clinical obesity, clinically underweight, renal disease, liver disease, blood disorder, other immunosuppressive conditions, organ transplant recipient, cancer, dementia, neurological/musculoskeletal disorder or Down's syndrome.

[4]CLI clinical discharge diagnosis codes include: COVID-19 U codes, COVID-19 pneumonia, influenza pneumonia, other viral pneumonia, pneumonia and influenza (bacterial and other) influenza diases, acute respiratory distress syndrome (ARDS), COPD exacerbation, asthma exacerbation, respiratory failure, other acute lower respiratory tract infection, sinusitis, acute upper respiratory tract infection.

[5]CLI signs and symptoms include: hemoptysis, cough, dyspnea unspecified, chest pain or breathing/painful respiration, asphyxia, hypoxemia, pleurisy, respiratory arrest, abnormal sputum, other specified symptoms and signs involving the circulatory and respiratory systems, fever, chills (without fever), diarrhea, disturbance of taste or smell, headache, myalgia, sepsis, other malaise, other fatigue, shock (unspecified), debility (unspecified), altered level of consciousness/mental state, weakness, nausea and vomiting, rash or other nonspecific skin eruption, abdominal pain.

Table S27. Characteristics of vaccinated and unvaccinated adults with medically attended COVID-19-like illness stratified by SARS-CoV-2 testing status within 14 days prior to, or within <72 hours after, the time of hospital admission or emergency department or urgent care visit

		Tested for SARS-CoV-2			Not Tested for SARS-CoV-2		
	Total Medical Events	**Vaccinated**	**Not Vaccinated**		**Vaccinated**	**Not Vaccinated**	
	N (Col. %)	N (Row %)	N (Row %)	**SMD**	N (Row %)	N (Row %)	**SMD**
A. Hospitalizations							
All hospitalizations	38130 (100)	10364 (40)	15299 (60)		6127 (49)	6340 (51)	
Sites				0.35			0.32
HealthPartners	1046 (3)	600 (61)	389 (39)		21 (37)	36 (63)	
Intermountain Healthcare	6611 (17)	1993 (51)	1917 (49)		1596 (59)	1105 (41)	
Kaiser Permanente Northwest	2107 (6)	1046 (54)	907 (46)		82 (53)	72 (47)	
Regenstrief Institute	22597 (59)	5272 (39)	8224 (61)		4377 (48)	4724 (52)	
University of Colorado	5769 (15)	1453 (27)	3862 (73)		51 (11)	403 (89)	
Age groups				0.36			0.36
50-64 years	9168 (24)	1673 (27)	4440 (73)		1074 (35)	1981 (65)	
65-74 years	12076 (32)	3214 (39)	4990 (61)		1851 (48)	2021 (52)	
75-84 years	10918 (29)	3455 (47)	3851 (53)		2029 (56)	1583 (44)	
≥85 years	5968 (16)	2022 (50)	2018 (50)		1173 (61)	755 (39)	
Sex				0.06			0.06
Male	18111 (47)	4782 (39)	7486 (61)		2778 (48)	3065 (52)	
Female	20018 (52)	5582 (42)	7812 (58)		3349 (51)	3275 (49)	
Other/unknown	1 (0)	0 (0)	1 (100)				
Race (regardless of ethnicity)				0.18			0.22
White	29615 (78)	8420 (42)	11562 (58)		5003 (52)	4630 (48)	
Black	2488 (7)	485 (25)	1448 (75)		208 (37)	347 (63)	
Other[1]	803 (2)	261 (41)	380 (59)		72 (44)	90 (56)	
Unknown	5224 (14)	1198 (39)	1909 (61)		844 (40)	1273 (60)	
Ethnicity (regardless of race)				0.10			0.17
Hispanic	1394 (4)	281 (26)	799 (74)		108 (34)	206 (66)	
Non-Hispanic	31561 (83)	8862 (41)	12836 (59)		5075 (51)	4788 (49)	
Unknown	5175 (14)	1221 (42)	1664 (58)		944 (41)	1346 (59)	

Admitting Hospital Type				0.05		0.13
Community	14108 (37)	3600 (41)	5278 (59)		2742 (52)	2488 (48)
Tertiary	21672 (57)	6285 (40)	9283 (60)		2888 (47)	3216 (53)
Unknown	2350 (6)	479 (39)	738 (61)		497 (44)	636 (56)
Urban-Rural Classification of Facility				0.09		0.10
Large Central Metro/Large Fringe Metro	18036 (47)	5583 (42)	7687 (58)		2474 (52)	2292 (48)
Medium Metro/Small Metro	15315 (40)	3896 (38)	6231 (62)		2525 (49)	2663 (51)
Micropolitan/Non-Core	2372 (6)	378 (38)	622 (62)		626 (46)	746 (54)
Unknown	2407 (6)	507 (40)	759 (60)		502 (44)	639 (56)
Underlying respiratory condition at discharge				-0.02		-0.03
Chronic respiratory condition[2]	21671 (57)	6121 (40)	9196 (60)		3069 (48)	3285 (52)
None	16459 (43)	4243 (41)	6103 (59)		3058 (50)	3055 (50)
Underlying non-respiratory condition at discharge				0.08		0.06
Chronic non-respiratory condition[3]	32348 (85)	9100 (41)	13018 (59)		5099 (50)	5131 (50)
None	5782 (15)	1264 (36)	2281 (64)		1028 (46)	1209 (54)
COVID-19-like illness (CLI) ICD discharge codes				-0.12		-0.11
≥1 CLI clinical diagnosis code[4]	24480 (64)	6686 (38)	10745 (62)		3290 (47)	3759 (53)
No clinical diagnosis but ≥1 CLI sign or symptom[5]	13650 (36)	3678 (45)	4554 (55)		2837 (52)	2581 (48)
CLI diagnosis and placement among discharge codes				-0.12		-0.14
CLI is first or primary diagnosis	12913 (34)	3150 (36)	5549 (64)		1868 (44)	2346 (56)
CLI is not first or primary diagnosis	25217 (66)	7214 (43)	9750 (57)		4259 (52)	3994 (48)
Intensive care unit (ICU) admissions				-0.13		-0.07
Admitted to ICU	6128 (16)	1574 (34)	3070 (66)		656 (44)	828 (56)
Not in ICU during hospitalization	32002 (84)	8790 (42)	12229 (58)		5471 (50)	5512 (50)
COVID-19 Vaccinations						
Unvaccinated	21639 (57)	0 (0)	15299 (100)		0 (0)	6340 (100)
BNT162b2 (Pfizer-BioNTech)	7865 (21)	5143 (100)	0 (0)		2722 (100)	0 (0)
mRNA-1273 (Moderna)	8151 (21)	4933 (100)	0 (0)		3218 (100)	0 (0)

Ad26.COV2.S (Johnson & Johnson)	475 (1)	288 (100)	0 (0)		187 (100)	0 (0)	
B. Emergency Department (ED) and Urgent Care (UC) Visits							
All ED and UC Visits	71866 (100)	10005 (45)	12316 (55)		27509 (56)	22035 (44)	
-	-	-	-	-	-	-	-
By medical event setting				0.14			0.21
ED visits	59616 (83)	8310 (43)	10844 (57)		21475 (53)	18987 (47)	
UC visits	12250 (17)	1695 (54)	1472 (46)		6034 (66)	3048 (34)	
Sites				0.33			0.33
Intermountain Healthcare	29466 (41)	4388 (49)	4620 (51)		12697 (62)	7761 (38)	
Kaiser Permanente Northwest	11441 (16)	2591 (55)	2121 (45)		4333 (64)	2395 (36)	
Regenstrief Institute	30959 (43)	3026 (35)	5575 (65)		10479 (47)	11879 (53)	
Age groups				0.41			0.35
50-64 years	26589 (37)	2539 (33)	5135 (67)		8513 (45)	10402 (55)	
65-74 years	21715 (30)	3134 (46)	3668 (54)		8676 (58)	6237 (42)	
75-84 years	16192 (23)	2949 (55)	2451 (45)		7022 (65)	3769 (35)	
≥85 years	7370 (10)	1383 (57)	1062 (43)		3298 (67)	1627 (33)	
Sex				0.04			0.06
Male	30090 (42)	4417 (44)	5689 (56)		10793 (54)	9191 (46)	
Female	41772 (58)	5588 (46)	6626 (54)		16715 (57)	12842 (43)	
Other/unknown	4 (0)	0 (0)	1 (100)		1 (33)	2 (67)	
Race (regardless of ethnicity)				0.22			0.24
White	57192 (80)	8396 (47)	9603 (53)		22748 (58)	16444 (42)	
Black	2758 (4)	244 (28)	625 (72)		783 (41)	1106 (59)	
Other[1]	1965 (3)	351 (47)	393 (53)		734 (60)	487 (40)	
Unknown	9951 (14)	1014 (37)	1695 (63)		3244 (45)	3998 (55)	
Ethnicity (regardless of race)				0.14			0.18
Hispanic	3749 (5)	453 (38)	731 (62)		1337 (52)	1228 (48)	
Non-Hispanic	57984 (81)	8553 (46)	9909 (54)		22848 (58)	16673 (42)	
Unknown	10133 (14)	999 (37)	1676 (63)		3324 (45)	4134 (55)	
Urban-Rural Classification of Facility				0.14			0.16
Large Central Metro/Large Fringe Metro	28458 (40)	4537 (47)	5043 (53)		11160 (59)	7717 (41)	

Medium Metro/Small Metro	29066 (40)	3968 (44)	4957 (56)		11114 (55)	9027 (45)	
Micropolitan/Non-Core	9943 (14)	938 (37)	1588 (63)		3542 (48)	3875 (52)	
Unknown	4399 (6)	562 (44)	728 (56)		1693 (54)	1416 (46)	
Underlying respiratory condition at discharge				0.08			0.04
Chronic respiratory condition[2]	18577 (26)	3653 (48)	4025 (52)		6243 (57)	4656 (43)	
None	53289 (74)	6352 (43)	8291 (57)		21266 (55)	17379 (45)	
Underlying non-respiratory condition at discharge				0.17			0.10
Chronic non-respiratory condition[3]	36403 (51)	6354 (48)	6785 (52)		13525 (58)	9738 (42)	
None	35463 (49)	3651 (40)	5531 (60)		13984 (53)	12297 (47)	
COVID-19-like illness (CLI) ICD discharge codes				-0.16			-0.01
≥1 CLI clinical diagnosis code[4]	28121 (39)	5001 (41)	7106 (59)		8834 (55)	7180 (45)	
No clinical diagnosis but ≥1 CLI sign or symptom[5]	43745 (61)	5004 (49)	5210 (51)		18675 (56)	14855 (44)	
CLI diagnosis and placement among discharge codes				-0.26			-0.10
CLI is first or primary diagnosis	37144 (52)	4569 (39)	7191 (61)		13512 (53)	11872 (47)	
CLI is not first or primary diagnosis	34722 (48)	5436 (51)	5125 (49)		13997 (58)	10163 (42)	
COVID-19 Vaccinations							
Unvaccinated	34351 (48)	0 (0)	12316 (100)		0 (0)	22035 (100)	
BNT162b2 (Pfizer-BioNTech)	19295 (27)	5347 (100)	0 (0)		13948 (100)	0 (0)	
mRNA-1273 (Moderna)	16312 (23)	4194 (100)	0 (0)		12118 (100)	0 (0)	
Ad26.COV2.S (Johnson & Johnson)	1907 (3)	464 (100)	0 (0)		1443 (100)	0 (0)	

Note: All patients with indeterminate immunization status (receipt of dose-1 of mRNA vaccine or J&J vaccine 1-13 days prior to index test date) were excluded from this table. Patients with SARS-CoV-2 testing, but only indeterminate or unknown result(s), are considered tested for the purpose of this table.

Abbreviations: Standard Mean Difference (SMD), COVID-like Illness (CLI), International Classification of Disease (ICD), Intensive Care Unit (ICU), Emergency Department (ED), Urgent Care (UC)

[1]Other race include Asian, Hawaiian or Other Pacific islander, American Indian or Alaskan Native, Other not-listed and multi-race.

[2]Underlying chronic respiratory conditions include asthma, chronic obstructive pulmonary disease (COPD), other lung disease.

[3]Underlying chronic non-respiratory conditions include heart failure, ischemic heart disease, hypertension, other heart disease, stroke, other cerebrovascular disease, diabetes (type 1, 2 and due to other specified conditions), other metabolic disease, clinical obesity, clinically underweight, renal disease, liver disease, blood disorder, other immunosuppressive conditions, organ transplant recipient, cancer, dementia, neurological/musculoskeletal disorder or Down's syndrome.

[4]CLI clinical discharge diagnosis codes include: COVID-19 U codes, COVID-19 pneumonia, influenza pneumonia, other viral pneumonia, pneumonia and influenza (bacterial and other) influenza disease, acute respiratory distress syndrome (ARDS), COPD exacerbation, asthma exacerbation, respiratory failure, other acute lower respiratory tract infection, sinusitis, acute upper respiratory tract infection.

[5]CLI signs and symptoms include: hemoptysis, cough, dyspnea unspecified, chest pain or breathing/painful respiration, asphyxia, hypoxemia, pleurisy, respiratory arrest, abnormal sputum, other specified symptoms and signs involving the circulatory and respiratory systems, fever, chills (without fever), diarrhea, disturbance of taste or smell, headache, myalgia, sepsis, other malaise, other fatigue, shock (unspecified), debility (unspecified), altered level of consciousness/mental state, weakness, nausea and vomiting, rash or other nonspecific skin eruption, abdominal pain.

Table_S28. messenger RNA (mRNA) vaccine effectiveness (VE) against COVID-19-associated hospitalization and emergency department and urgent care (ED/UC) medical events after accounting for likelihood of testing

				VE before Adjusted Model		VE using primary model without adjustment for testing		VE with inverse weights for propensity to be vaccinated multiplied by propensity to be clinically tested	
	Total	SARS-CoV-2 Positive	Row %	%	95% CI	%	95% CI	%	95% CI
mRNA VE against COVID-19 hospitalization[1]									
VE both mRNA vaccines (aged ≥50 years)									
Unvaccinated (Referent)	14666	2612	17.8						
Partially 1-Dose Vaccinated	1846	145	7.8	61	53 - 67	57	48 - 64	59	48 - 67
Partially 2-Dose Vaccinated	1399	70	5.0	76	69 - 81	72	63 - 79	75	66 - 81
Fully Vaccinated	6412	142	2.2	90	88 - 91	90	87 - 91	88	85 - 90
mRNA VE against COVID-19 ED/UC									
VE both mRNA vaccines (aged ≥50 years)									
Unvaccinated (Referent)	11812	2847	24.1						
Partially 1-Dose Vaccinated	1920	155	8.1	72	67 - 77	68	61 - 74	70	62 - 75
Partially 2-Dose Vaccinated	1269	66	5.2	83	78 - 87	80	73 - 85	83	76 - 88
Fully Vaccinated	6065	154	2.5	92	90 - 93	91	89 - 93	91	88 - 92

[1]Hospitalization estimates do not include KPNC or CU

E. Messenger RNA COVID-19 Vaccine Effectiveness among COVID-19-associated Emergency Department and Urgent Care Encounters

1. Variables included in inverse propensity to be vaccinated weights for ED/UC

In examining the association with COVID-19 infection status, the variables that had a SMD of >0.1, and thus were potential confounders included in the inverse-propensity-to-be-vaccinated weights, were site-region, race, ethnicity, age, urban-rural classification of the facility, underlying conditions (including specific conditions), and 7-day moving average percent positivity (Table S29). Epidemiologic days was included as an *a priori* decision. Of these variables, site-region, age, race, ethnicity, several underlying medical conditions, and epidemiologic days were also unbalanced by vaccination status (SMD of >0.1 in a bivariate association with vaccination before their inclusion in the propensity to be vaccinated weights).

The distribution of weights from each of the VE models for ED/UC is presented in Table S30. Across models, outliers were at the extreme upper ends of the distributions. Therefore, weights were truncated at the 99.9 percentile for each model. Table S30 lists the relatively small number of medical events in each model that received the truncated weight.

After inverse-propensity-to-be-vaccinated weighting, all variables were balanced across the vaccinated and unvaccinated groups (all with SMD <0.05); see Table S31.

VE estimates were similar to VE estimates before adjustment, with most having <10% difference (Table S19). The largest differences between VE estimates before and after adjustments were seen for estimates for the partial 1-dose vaccinations.

Table S29. Bivariate associations between covariates of interest and COVID-19 infection status for emergency department and urgent care medical events

	Sample		SARS-CoV-2 Negatives		SARS-CoV-2 Positives			
	N	(Col. %)	N	(Row %)	N	(Row %)	SMD[1]	Is variable included in Propensity Model[2]
A. Emergency department and urgent care								
All emergency department and urgent care medical events	21066	(100)	17844	(84.7)	3222	(15.3)		
Site Characteristics								
Site-region							0.42	Yes
Intermountain Healthcare - site-region 1	593	(2.8)	510	(86.0)	83	(14.0)		
Intermountain Healthcare - site-region 2	353	(1.7)	275	(77.9)	78	(22.1)		
Intermountain Healthcare - site-region 3	3185	(15.1)	2792	(87.7)	393	(12.3)		
Intermountain Healthcare - site-region 4	1402	(6.7)	1150	(82.0)	252	(18.0)		
Intermountain Healthcare - site-region 5	302	(1.4)	254	(84.1)	48	(15.9)		
Intermountain Healthcare - site-region 6	1113	(5.3)	951	(85.4)	162	(14.6)		
Intermountain Healthcare - site-region 7	278	(1.3)	236	(84.9)	42	(15.1)		
Intermountain Healthcare - site-region 8	1551	(7.4)	1229	(79.2)	322	(20.8)		
Kaiser Permanente Northwest - site-region 1	2122	(10.1)	1930	(91.0)	192	(9.0)		
Kaiser Permanente Northwest - site-region 2	1912	(9.1)	1768	(92.5)	144	(7.5)		
Kaiser Permanente Northwest - site-region 3	535	(2.5)	470	(87.9)	65	(12.1)		
Regenstrief Institute - site-region 1	885	(4.2)	697	(78.8)	188	(21.2)		
Regenstrief Institute - site-region 2	191	(0.9)	179	(93.7)	12	(6.3)		
Regenstrief Institute - site-region 3	504	(2.4)	408	(81.0)	96	(19.0)		
Regenstrief Institute - site-region 4	289	(1.4)	154	(53.3)	135	(46.7)		
Regenstrief Institute - site-region 5	870	(4.1)	684	(78.6)	186	(21.4)		
Regenstrief Institute - site-region 6	2299	(10.9)	1930	(83.9)	369	(16.1)		
Regenstrief Institute - site-region 7	631	(3.0)	522	(82.7)	109	(17.3)		
Regenstrief Institute - site-region 8	173	(0.8)	150	(86.7)	23	(13.3)		
Regenstrief Institute - site-region 9	700	(3.3)	572	(81.7)	128	(18.3)		
Regenstrief Institute - site-region 10	391	(1.9)	338	(86.4)	53	(13.6)		
Regenstrief Institute - site-region missing	787	(3.7)	645	(82.0)	142	(18.0)		
Patient Characteristics								
Sex								
Female	11489	(54.5)	9862	(85.8)	1627	(14.2)	0.1	No
Male	9577	(45.5)	7982	(83.3)	1595	(16.6)		
Race							0.17	Yes

White	17191	(	81.6	)	14738	(	85.7	)	2453	(	14.3	)
Black	818	(	3.9	)	641	(	78.4	)	177	(	21.6	)
Other[3]	724	(	3.4	)	609	(	84.1	)	115	(	15.9	)
Unknown	2333	(	11.1	)	1856	(	79.6	)	477	(	20.4	)
Ethnicity											0.21	Yes
Hispanic/Latinx Ethnicity	1142	(	5.4	)	852	(	74.6	)	290	(	25.4	)
Not Hispanic/Latinx Ethnicity	17762	(	84.3	)	15247	(	85.8	)	2515	(	14.2	)
Unknown	2162	(	10.3	)	1745	(	80.7	)	417	(	19.3	)
Age, continuous (mean, std)	69.9	(	11.4	)	70.54	(	11.4	)	66.34	(	10.8	)	0.38	Yes
Setting Characteristics											0.21	Yes
Urban-Rural Classification of Facility	9252	(	43.9	)	8072	(	87.2	)	1180	(	12.8	)
Large Central Metro/Large Fringe Metro	8420	(	40.0	)	7045	(	83.7	)	1375	(	16.3	)
Medium Metro/Small Metro	2228	(	10.6	)	1746	(	78.4	)	482	(	21.6	)
Micropolitan/Non-Core	1166	(	5.5	)	981	(	84.1	)	185	(	15.9	)
Unknown												
Underlying medical conditions (more than one may apply)												
Chronic respiratory condition	7204	(	34.2	)	6427	(	89.2	)	777	(	10.8	)	0.26	Yes
Chronic non-respiratory condition	12405	(	58.9	)	10914	(	88.0	)	1491	(	12.0	)	0.3	Yes
Asthma	1395	(	6.6	)	1263	(	90.5	)	132	(	9.5	)	0.13	Yes
COPD	3548	(	16.8	)	3358	(	94.6	)	190	(	5.4	)	0.4	Yes
Other Chronic Lung Disease	3818	(	18.1	)	3228	(	84.5	)	590	(	15.5	)	0.01	No
Heart Failure	3037	(	14.4	)	2851	(	93.9	)	186	(	6.1	)	0.33	Yes
Ischemic Heart Disease	2965	(	14.1	)	2713	(	91.5	)	252	(	8.5	)	0.23	Yes
Hypertension	7700	(	36.6	)	6888	(	89.5	)	812	(	10.5	)	0.29	Yes
Other Heart Disease	5667	(	26.9	)	5158	(	91.0	)	509	(	9.0	)	0.32	Yes
Stroke	449	(	2.1	)	422	(	94.0	)	27	(	6.0	)	0.12	Yes
Other CD	333	(	1.6	)	306	(	91.9	)	27	(	8.1	)	0.08	No
Type 1 Diabetes	95	(	0.5	)	87	(	91.6	)	8	(	8.4	)	0.04	No
Type 2 Diabetes	3974	(	18.9	)	3482	(	87.6	)	492	(	12.4	)	0.11	Yes
Other Diabetes	53	(	0.3	)	48	(	90.6	)	5	(	9.4	)	0.03	No
Other Metabolic Disease (excluding diabetes)	5933	(	28.2	)	5282	(	89.0	)	651	(	11.0	)	0.22	Yes
Clinical Obesity	2343	(	11.1	)	2011	(	85.8	)	332	(	14.2	)	0.03	No
Clinical Underweight	738	(	3.5	)	665	(	90.1	)	73	(	9.9	)	0.09	No
Renal Disease	3317	(	15.7	)	3037	(	91.6	)	280	(	8.4	)	0.25	Yes
Liver	846	(	4.0	)	769	(	90.9	)	77	(	9.1	)	0.11	Yes
Blood	740	(	3.5	)	656	(	88.6	)	84	(	11.4	)	0.06	No

Immunosuppression	4147	(	19.7	)	3717	(	89.6	)	430	(	10.4	)	0.2	Yes
Organ Transplant	133	(	0.6	)	114	(	85.7	)	19	(	14.3	)	0.01	No
Cancer	1065	(	5.1	)	975	(	91.5	)	90	(	8.5	)	0.14	Yes
Dementia	1034	(	4.9	)	944	(	91.3	)	90	(	8.7	)	0.13	Yes
Other Neurological/Musculoskeletal Disorder	3322	(	15.8	)	3048	(	91.8	)	274	(	8.2	)	0.26	Yes
Down Syndrome	4	(	0.0	)	4	(	100.0	)	0	(	0.0	)	0.02	No
Time Considerations (Median, Q1-Q3)														
Epi-curve (days)	4/19		3/22-5/16		4/18		3/22-5/15		4/21		3/24-5/16		0.01	Yes
7-day Moving Average Percent Positivity (%)	4.77		3.76-6.06		4.72		3.67-5.89		5.3		4.25-7.05		0.34	Yes

[1]Illustrates SMD prior to propensity weighting, to show differences between SARS-CoV-2 negative and positive groups.

[2]Variables with a SMD > 0.1 were included in PS weighting.

[3]Other race include: Asian, Hawaiian or Other Pacific islander, American Indian or Alaskan Native, Other not-listed and multi-race.

Table S30. Quantiles of Inverse Propensity to be Vaccinated Weights used for ED/UC VE Estimates

	50%	Min	Max	1%	25%	75%	99%	99.90%	Number of Events Truncated to the 99.9% Weight
mRNA VE among COVID-19 ED/UC medical events									
VE both mRNA vaccines (aged ≥50 years)	1.648	1.017	21.369	1.072	1.382	2.225	4.865	8.515	22
By vaccine product among COVID-19 medical events									
VE of BioNTech-Pfizer mRNA (aged ≥50 years)	1.445	1.008	27.957	1.036	1.223	1.996	6.421	13.306	18
VE of Moderna mRNA (aged ≥50 years)	1.426	1.013	19.984	1.040	1.198	1.954	6.939	13.453	16
Ad26.COV2.S (Johnson & Johnson)	1.038	1.003	95.733	1.003	1.005	1.076	16.684	42.097	13
By Age Group among COVID-19 medical events									
VE both mRNA vaccines (aged 50-64 years)	1.628	1.042	16.233	1.080	1.353	2.052	5.099	8.636	8
VE both mRNA vaccines (aged 65-74 years)	1.682	1.013	14.381	1.048	1.362	2.176	5.222	8.776	7
VE both mRNA vaccines (aged 75-84 years)	1.506	1.017	17.077	1.062	1.287	2.133	5.780	8.185	6
VE both mRNA vaccines (aged ≥85 years)	1.558	1.040	10.813	1.099	1.341	2.115	4.631	7.998	3
By Race and Ethnicity among COVID-19 medical events									
VE both mRNA vaccines among White adults aged ≥50 years	1.637	1.029	17.815	1.083	1.375	2.239	4.878	7.711	18
VE both mRNA vaccines among Black adults aged ≥50 years	1.383	1.048	14.063	1.069	1.194	1.715	6.027	11.497	1
VE both mRNA vaccines among Other or Unknown aged ≥50 years	1.642	1.016	8.799	1.066	1.387	2.074	4.369	7.448	4
VE both mRNA vaccines among Hispanic adults aged ≥50 years	1.474	1.032	9.025	1.062	1.282	1.926	5.683	8.579	2
VE both mRNA vaccines among Non-Hispanic adults aged ≥50 years	1.645	1.014	23.592	1.070	1.377	2.228	4.955	8.569	20
By Presence of Absence of Underlying Chronic Medical Conditions Associated with Increased Risk of Severe Respiratory Disease									
VE both mRNA vaccines among aged ≥50 years with no chronic condition	1.585	1.020	18.042	1.073	1.332	2.153	5.768	9.935	8
VE both mRNA vaccines among aged ≥50 years with ≥1 chronic respiratory condition	1.666	1.033	13.932	1.085	1.386	2.207	4.738	7.101	8
VE both mRNA vaccines among aged ≥50 years with ≥1 chronic non-respiratory condition	1.667	1.033	15.301	1.083	1.403	2.233	4.597	6.846	13
By Alternative Clinical Outcomes									

VE both mRNA vaccines among aged ≥50 years with acute respiratory illness diagnosis	1.661	1.022	17.470	1.068	1.374	2.221	4.921	8.154	12
VE both mRNA vaccines among aged ≥50 years with clinical pneumonia diagnosis	1.598	1.039	7.740	1.074	1.345	2.150	5.206	6.969	4
VE both mRNA vaccines among aged ≥50 years with CLI/signs and symptoms as primary discharge code	1.626	1.018	14.132	1.075	1.357	2.170	4.986	8.125	12

2. ED/UC VE Sensitivity Analysis: Between Partner Heterogeneity

In a sensitivity analysis examining potential heterogeneity in the VE estimates across partners, mRNA VE estimates among COVID-19 ED/UC encounters were similar (range=89%-97% for full vaccination, 77%-81% for partial 2-dose vaccination, and 60%-74% for partial 1-dose vaccination) (Table S17). Because only 3 partners contributed to ED/UC analyses, χ^2 (or Q-test) and I^2 index were not calculated.

3. ED/UC VE Sensitivity Analysis: Alternative Clinical Outcomes

In a sensitivity analysis to explore possible heterogeneity in VE by alternative clinical outcome, the mRNA VE among ED/UC encounters with clinical pneumonia diagnosis was 95% (95%CI=93%-97%) for full vaccination, 87% (95%CI=76%-93%) for partial 2-dose vaccination, and 76% (95%CI=64%-84%) for partial 1-dose vaccination. The mRNA VE among ED/UC encounters with CLI as the primary discharge code was 91% (95%CI=89%-93%) for full vaccination, 83% (95%CI=76%-88%) for partial 2-dose vaccination, and 68% (95%CI=60%-74%) for partial 1-dose vaccination (Table S19). As a whole, the mRNA VE estimates for both alternative clinical outcomes were similar and had overlapping confidence intervals relative to the main mRNA VE estimates among COVID-19 ED/UC encounters.

4. ED/UC VE Sensitivity Analysis: Exclude Historical SARS-CoV-2 Positives

In a sensitivity analysis excluding patients with any SARS-CoV-2 positive result from molecular or antigen assays >14 days prior to the index date, the mRNA VE among COVID-19 ED/UC encounters was 92% (95%CI=90%-93%) for full vaccination, 83% (95%CI=77%-87%) for partial 2-dose vaccination, and 68% (95%CI=61%-74%) for partial 1-dose vaccination (Table S25). These estimates were very similar to VE estimates in the main analysis (differences of ≤3% points).

5. ED/UC VE Sensitivity Analysis: Propensity of Clinical Testing for SARS-CoV-2

In a sensitivity analysis to examine potential bias introduced by clinician-ordered testing, IPW were calculated to account for both propensity to be vaccinated and propensity to be tested. The model for propensity for vaccination was build using only those who tested negative for SARS-CoV-2, while the model for propensity for testing was built with all the data. Among 71,866 CLI ED/UC encounters, 22,321 (31%) had available test results for SARS-CoV-2 across three partners (IH, KPNW, and RG; Table S26). Among ED/UC encounters, testing percentage varied by site ranging from 28% within RG to 41% within KPNW. Higher testing percentages were seen in encounters with chronic respiratory conditions (41%) or chronic non-respiratory conditions (36%), unvaccinated individuals (36% compared to 24-28% who received any of the COVID-19 vaccines), or those with CLI diagnosis code (41%).

The proportion of vaccination varied by partner, age, race, and ethnicity; this variation was similar among both those tested and those not tested for SARS-CoV-2 (Table S27).

The mRNA VE estimates among COVID-19 ED/UC encounters accounting for testing and vaccination were 91% (95%CI=88%-92%) for full vaccination, 83% (95%CI=76%-88%) for partial 2-dose vaccination, and 70% (95%CI=62%-75%) for partial 1-dose vaccination (Table S28). In comparison, the mRNA VE estimates in the main analysis were 91% (95%CI=89%-93%) for full vaccination, 80% (95%CI=73%-85%) for partial 2-dose vaccination, and 68% (95%CI=61%-74%) for partial 1-dose vaccination. The VE estimates using these different inverse propensity weights were similar to the results of the main analysis for full and partial 2-dose vaccination (difference ≤3% points) (Table S31).

Table S31 . Unweighted and weighted standardized mean differences (SMD) for variables included in PS model1 for unvaccinated and mRNA vaccinees only - Emergency department and urgent care medical events

	Unvaccinated		Partially or Fully Vaccinated		Unweighted	Weighted
	N	Row %	N	Row %	SMD[2]	SMD[3]
A. Emergency department and urgent care						
All emergency department and urgent care medical events	8965	50.2	8879	49.8		
Site Characteristics						
Site-region						
Intermountain Healthcare - site-region 1	202	39.6	308	60.4	0.073	0.006
Intermountain Healthcare - site-region 2	123	44.7	152	55.3	0.028	0.003
Intermountain Healthcare - site-region 3	1208	43.3	1584	56.7	0.120	0.007
Intermountain Healthcare - site-region 4	506	44.0	644	56.0	0.066	0.002
Intermountain Healthcare - site-region 5	121	47.6	133	52.4	0.013	0.002
Intermountain Healthcare - site-region 6	490	51.5	461	48.5	-0.012	-0.001
Intermountain Healthcare - site-region 7	120	50.8	116	49.2	-0.003	0.005
Intermountain Healthcare - site-region 8	649	52.8	580	47.2	-0.028	-0.007
Kaiser Permanente Northwest - site-region 1	746	38.7	1184	61.3	0.161	0.014
Kaiser Permanente Northwest - site-region 2	790	44.7	978	55.3	0.074	0.002
Kaiser Permanente Northwest - site-region 3	210	44.7	260	55.3	0.037	0.002
Regenstrief Institute - site-region 1	489	70.2	208	29.8	-0.161	-0.014
Regenstrief Institute - site-region 2	228	55.9	180	44.1	-0.035	-0.007
Regenstrief Institute - site-region 3	100	64.9	54	35.1	-0.055	-0.010
Regenstrief Institute - site-region 4	407	59.5	277	40.5	-0.074	-0.008
Regenstrief Institute - site-region 5	1116	57.8	814	42.2	-0.106	0.003
Regenstrief Institute - site-region 6	343	65.7	179	34.3	-0.107	-0.010
Regenstrief Institute - site-region 7	100	66.7	50	33.3	-0.060	-0.006
Regenstrief Institute - site-region 8	364	63.6	208	36.4	-0.098	0.000
Regenstrief Institute - site-region 9	186	55.0	152	45.0	-0.027	-0.001
Regenstrief Institute - site-region 10	101	56.4	78	43.6	-0.025	-0.003
Regenstrief Institute - site-region Missing	366	56.7	279	43.3	-0.050	-0.003
Patient Characteristics						
Sex						
Female	4895	49.6	4967	50.4		
Male	4070	51.0	3912	49.0		

Race									
White	7176	(	48.7	)	7562	(	51.3	)	0.135	0.014
Black	438	(	68.3	)	203	(	31.7	)	-0.140	-0.009
Other[4]	292	(	47.9	)	317	(	52.1	)	0.017	0.002
Unknown	1059	(	57.1	)	797	(	42.9	)	-0.093	-0.013
Ethnicity										
Hispanic/Latinx Ethnicity	7494	(	49.2	)	7753	(	50.8	)	0.106	0.014
Not Hispanic/Latinx Ethnicity	477	(	56.0	)	375	(	44.0	)	-0.051	-0.010
Unknown	994	(	57.0	)	751	(	43.0	)	-0.089	-0.010
Age, continuous (mean, std)	68.55	(	11.5	)	72.56	(	11.0	)	0.352	0.018
Setting Characteristics										
Urban-Rural Classification of Facility										
Large Central Metro/Large Fringe Metro	3928	(	48.7	)	4144	(	51.3	)	0.057	0.008
Medium Metro/Small Metro	3545	(	50.3	)	3500	(	49.7	)	-0.003	-0.003
Micropolitan/Non-Core	985	(	56.4	)	761	(	43.6	)	-0.081	-0.003
Unknown	507	(	51.7	)	474	(	48.3	)	-0.014	-0.005
Underlying medical conditions (more than one may apply)										
Chronic respiratory condition	3155	(	49.1	)	3272	(	50.9	)	0.035	-0.003
Chronic non-respiratory condition	5190	(	47.6	)	5724	(	52.4	)	0.135	-0.001
Asthma	557	(	44.1	)	706	(	55.9	)	0.068	0.005
COPD	1811	(	53.9	)	1547	(	46.1	)	-0.071	-0.017
Other Chronic Lung Disease	1420	(	44.0	)	1808	(	56.0	)		
Heart Failure	1362	(	47.8	)	1489	(	52.2	)	0.043	-0.004
Ischemic Heart Disease	1246	(	45.9	)	1467	(	54.1	)	0.073	-0.004
Hypertension	3176	(	46.1	)	3712	(	53.9	)	0.131	0.007
Other Heart Disease	2381	(	46.2	)	2777	(	53.8	)	0.104	0.004
Stroke	186	(	44.1	)	236	(	55.9	)	0.038	0.000
Other CD	141	(	46.1	)	165	(	53.9	)		
Type 1 Diabetes	27	(	31.0	)	60	(	69.0	)		
Type 2 Diabetes	1616	(	46.4	)	1866	(	53.6	)	0.075	0.010
Other Diabetes	20	(	41.7	)	28	(	58.3	)		
Other Metabolic Disease (excluding diabetes)	2369	(	44.9	)	2913	(	55.1	)	0.140	0.017
Clinical Obesity	917	(	45.6	)	1094	(	54.4	)		
Clinical Underweight	349	(	52.5	)	316	(	47.5	)		
Renal Disease	1304	(	42.9	)	1733	(	57.1	)	0.132	0.016

Liver	395	(	51.4	)	374	(	48.6	)	-0.010	-0.008
Blood	272	(	41.5	)	384	(	58.5	)		
Immunosuppression	1655	(	44.5	)	2062	(	55.5	)	0.117	0.016
Organ Transplant	52	(	45.6	)	62	(	54.4	)		
Cancer	466	(	47.8	)	509	(	52.2	)	0.024	-0.004
Dementia	382	(	40.5	)	562	(	59.5	)	0.092	0.009
Other Neurological/Musculoskeletal Disorder	1406	(	46.1	)	1642	(	53.9	)	0.075	-0.004
Down Syndrome	2	(	50.0	)	2	(	50.0	)		
Time Considerations (Median, Q1-Q3)										
Epi-curve (days)	4/09		3/12-5/10		4/24		3/30-5/18		0.359	0.044
7-day Moving Average Percent Positivity (days)	4.85		3.74-6.26		4.56		3.65-5.58		-0.238	-0.035

[1]Variables with a SMD > 0.1 in the pooled mRNA and J and J sample were included in PS weighting.

[2]Illustrates SMD prior to propensity weighting, to show differences between vaccinated and unvaccinated groups.

[3]SMD values after propensity weighting, SMD < 0.2 indicates no differences between groups, and that balance was achieved. Variables where balance was not achieved were included directly as covariates in the VE models.

[4]Other race include: Asian, Hawaiian or Other Pacific islander, American Indian or Alaskan Native, Other not-listed and multi-race.

F. Johnson & Johnson COVID-19 Vaccine Effectiveness

1. Adaptation of methods for product specific VE analysis

Due to the later date of FDA emergency use authorization for the Ad26.COV2.S (Janssen/Johnson & Johnson) [J&J] vaccine and the smaller numbers of patients who received this vaccine during the study period, the methods for the product-specific VE analysis was changed from the primary methods in four ways: (1) study start date began on the index date of first fully vaccinated J&J recipient for each respective partner, (2) any partner with fewer than five J&J vaccine recipients at the time of final data collection were excluded from the analysis, (3) site-regions were collapsed so that each site-region contained at least five J&J vaccine recipients, and (4) rather than examine underlying medical conditions as multiple separate conditions, two dichotomous variables (respiratory chronic conditions and non-respiratory chronic conditions) were examined.

With these changes, two sites were excluded from the hospitalization VE analysis: HP (only 2 J&J vaccine recipients) and UCO (no J&J vaccine recipients). No sites were excluded from the ED/UC encounter analysis. For RG, 10 site-regions were collapsed to 5 site-regions in this VE analysis. For IH, 8 site-regions were collapsed to 6 site-regions. KPNW was examined as a single site-region.

Instead of the vaccine eligibility dates listed in Table 1, the vaccine eligibility dates for the J&J VE analysis were as follows:

Hospitalizations

CUIMC: 03/27

IH: 03/25

KPNC: 03/25

KPNW: 03/25

RG: 03/22

ED/UC encounters

IH: 03/19

KPNW: 03/19

RG: 03/19

A total of 11,468 hospitalizations (Table S16) and 8,917 ED/UC encounters (Table S19) were included in the J&J VE analyses. Among hospitalizations, 707 (6%) were fully J&J vaccinated, compared to 456 (5%) of ED/UC encounters.

2. Variables included in inverse propensity to be vaccinated weights

In examining the association with COVID-19 infection status, the variables that had a SMD of >0.1, and thus were potential confounders included in the inverse-propensity-to-be-vaccinated weights, were site-region, race, ethnicity, age, urban-rural classification of the facility, underlying conditions, and 7-day moving average percent positivity (data not shown). Of these variables, site-region, race, ethnicity, age, urban-rural classification of the facility, epidemiologic days, and 7-day moving average percent positivity were also unbalanced by vaccination status (SMD of >0.1 in a bivariate association with vaccination before their inclusion in the propensity to be vaccinated weights) (Table S32 and Table S33). After inverse-propensity-to-be-vaccinated weighting, all variables were balanced across the vaccinated and unvaccinated groups (all with SMD <0.2). Calendar time was included in the multivariate logistic regression analysis for both hospitalizations and ED/UC encounters analyses.

Table S32. Unweighted and weighted standardized mean differences (SMD) for variables included in PS model[1] for unvaccinated and J&J vaccinees only - Hospitalization events

	Unvaccinated		Fully Vaccinated		Unweighted	Weighted
	N	Row %	N	Row %	SMD[2]	SMD[3]
A. Hospitalizations						
All Hospitalization events	8755	92.8	677	7.2		
Site Characteristics						
Site-region						
Columbia University - site-region 1	964	96.3	37	3.7	-0.18	0.015
Intermountain Healthcare - site-region 1	69	89.6	8	10.4	0.044	-0.005
Intermountain Healthcare - site-regions 2, 3	372	92.5	30	7.5	0.009	0.025
Intermountain Healthcare - site-region 4	177	96.7	6	3.3	-0.082	-0.043
Intermountain Healthcare - site-region 5	19	95.0	1	5.0	-0.015	-0.026
Intermountain Healthcare - site-region 6	127	91.4	12	8.6	0.027	0.003
Intermountain Healthcare - site-regions 7, 8	151	85.3	26	14.7	0.156	0.016
Kaiser Permanente Northern California - site-region 1	166	90.7	17	9.3	0.045	0.02
Kaiser Permanente Northern California - site-region 2	136	94.4	8	5.6	-0.03	-0.018
Kaiser Permanente Northern California - site-region 3	696	92.1	60	7.9	0.034	0.019
Kaiser Permanente Northern California - site-region 4	943	83.8	182	16.2	0.497	0.047
Kaiser Permanente Northern California - site-region 5	253	80.1	63	19.9	0.357	-0.001
Kaiser Permanente Northern California - site-region 6	95	81.9	21	18.1	0.183	0.017
Kaiser Permanente Northern California - site-region 7	66	94.3	4	5.7	-0.019	-0.016
Kaiser Permanente Northern California - site-region 8	224	90.0	25	10.0	0.071	0.011
Kaiser Permanente Northwest - site-region 1	350	88.6	45	11.4	0.132	0.016
Kaiser Permanente Northwest - site-region 2	64	92.8	5	7.2	0.001	0.004
Kaiser Permanente Northwest - site-region 3, 4, 5	43	97.7	1	2.3	-0.05	-0.034
Regenstrief Institute - site-regions 1,2,3	1219	97.1	36	2.9	-0.253	0.013
Regenstrief Institute - site-region 4	247	96.9	8	3.1	-0.101	-0.02
Regenstrief Institute - site-region 5	1072	96.4	40	3.6	-0.196	0.031
Regenstrief Institute - site-regions 6,9	515	96.3	20	3.7	-0.127	-0.064
Regenstrief Institute - site-regions 7,8,10	344	98.3	6	1.7	-0.161	-0.068
Regenstrief Institute - site-region missing	301	97.4	8	2.6	-0.127	-0.07
Patient Characteristics						
Sex					-	-
Female	4665	92.7	369	7.3		
Male	4090	93.0	308	7.0		

Race										
White	5648	(	92.9	)	434	(	7.1	)	-0.008	-0.036
Black	1157	(	93.5	)	81	(	6.5	)	-0.037	0.089
Other[4]	483	(	86.4	)	76	(	13.6	)	0.242	0.04
Unknown	1467	(	94.5	)	86	(	5.5	)	-0.109	-0.059
Ethnicity										
Hispanic/Latinx Ethnicity	987	(	92.4	)	81	(	7.6	)	-0.134	0.027
Not Hispanic/Latinx Ethnicity	6236	(	93.4	)	441	(	6.6	)	0.022	-0.032
Unknown	1532	(	90.8	)	155	(	9.2	)	0.141	-0.006
Age, continuous (mean, std)	69.99	(	50.1	)	69.61	(	49.9	)	-0.033	-0.04
Setting Characteristics										
Urban-Rural Classification of Facility										
Large Central Metro/Large Fringe Metro	5985	(	92.2	)	505	(	7.8	)	0.135	0.103
Medium Metro/Small Metro	2292	(	93.7	)	154	(	6.3	)	-0.078	-0.083
Micropolitan/Non-Core	162	(	95.3	)	8	(	4.7	)	-0.05	0.011
Unknown	316	(	96.9	)	10	(	3.1	)	-0.117	-0.068
Underlying medical conditions (more than one may apply)										
Chronic respiratory condition	5606	(	92.4	)	460	(	7.6	)	0.082	-0.005
Chronic non-respiratory condition	7708	(	92.3	)	645	(	7.7	)	0.227	0.079
Time Considerations (Median, Q1-Q3)										
Epi-curve (days)	4/28		4/11-5/19		05/10		4/25-5/28		0.457	0.133
7-day Moving Average Percent Positivity (%)	4.26		2.4-5.7		2.3		1.1-4.6		-0.543	-0.035

[1]Variables with a SMD > 0.1 in the pooled mRNA and J and J sample were included in PS weighting.

[2]Illustrates SMD prior to propensity weighting, to show differences between vaccinated and unvaccinated groups.

[3]SMD values after propensity weighting, SMD < 0.2 indicates no differences between groups, and that balance was achieved. Variables where balance was not achieved were included directly as covariates in the VE models.

[4]Other race include: Asian, Hawaiian or Other Pacific islander, American Indian or Alaskan Native, Other not-listed and multi-race.

Table S33. Unweighted and weighted standardized mean differences (SMD) for variables included in PS model[1] for unvaccinated and J&J vaccinees only - Emergency department and urgent care medical events

	Unvaccinated		Fully Vaccinated		Unweighted	Weighted
	N	(Row %)	N	(Row %)	SMD[2]	SMD[3]
A. Emergency department and urgent care						
All emergency department and urgent care medical events	6261	(93.6)	427	(6.4)		
Site Characteristics						
Site-region						
Intermountain Healthcare - site-region 1	161	(93.1)	12	(6.9)	0.015	-0.012
Intermountain Healthcare - site-region 2	991	(93.0)	75	(7.0)	0.047	0.034
Intermountain Healthcare - site-region 4	366	(95.8)	16	(4.2)	-0.090	0.000
Intermountain Healthcare - site-region 5	82	(91.1)	8	(8.9)	0.049	0.017
Intermountain Healthcare - site-region 6	377	(92.2)	32	(7.8)	0.061	0.001
Intermountain Healthcare - site-region 7	502	(89.3)	60	(10.7)	0.217	0.032
Kaiser Permanente Northwest - site-region 1	579	(88.7)	74	(11.3)	0.272	0.016
Kaiser Permanente Northwest - site-region 2	398	(93.9)	26	(6.1)	-0.011	0.027
Kaiser Permanente Northwest - site-region 3	166	(94.9)	9	(5.1)	-0.034	-0.004
Regenstrief Institute - site-region 1	594	(96.4)	22	(3.6)	-0.150	-0.039
Regenstrief Institute - site-region 4	269	(96.1)	11	(3.9)	-0.086	0.015
Regenstrief Institute - site-region 5	784	(95.4)	38	(4.6)	-0.110	0.027
Regenstrief Institute - site-region 6	370	(96.4)	14	(3.6)	-0.113	-0.088
Regenstrief Institute - site-region 7	350	(96.7)	12	(3.3)	-0.123	-0.040
Regenstrief Institute - site-region missing	272	(93.8)	18	(6.2)	-0.006	-0.015
Patient Characteristics						
Sex						
Female	3417	(93.4)	241	(6.6)		
Male	2844	(93.9)	186	(6.1)		
Race						
White	4902	(93.3)	351	(6.7)	0.095	0.039
Black	348	(96.1)	14	(3.9)	-0.101	-0.020
Other[4]	223	(93.3)	16	(6.7)	0.010	-0.049
Unknown	788	(94.5)	46	(5.5)	-0.055	-0.007
Ethnicity						
Hispanic/Latinx Ethnicity	5151	(93.5)	359	(6.5)	0.047	0.001

Not Hispanic/Latinx Ethnicity	377	(	93.8	)	25	(	6.2	)	-0.007	0.003
Unknown	733	(	94.5	)	43	(	5.5	)	-0.051	-0.003
Age, continuous (mean, std)	65.44	(	11.1	)	65.81	(	10.7	)	0.033	-0.021
Setting Characteristics										
Urban-Rural Classification of Facility										
Large Central Metro/Large Fringe Metro	2802	(	93.5	)	194	(	6.5	)	0.014	0.001
Medium Metro/Small Metro	2428	(	93.8	)	160	(	6.2	)	-0.027	-0.010
Micropolitan/Non-Core	646	(	93.8	)	43	(	6.2	)	-0.008	0.020
Unknown	385	(	92.8	)	30	(	7.2	)	0.036	-0.008
Underlying medical conditions (more than one may apply)										
Chronic respiratory condition	2155	(	92.6	)	171	(	7.4	)	0.118	0.035
Chronic non-respiratory condition	3419	(	93.4	)	243	(	6.6	)	0.046	-0.011
Time Considerations (Median, Q1-Q3)										
Epi-curve (days)	4/28		4/7-5/19		5/09		4/22-5/26		0.390	0.059
7-day Moving Average Percent Positivity (%)	4.74		3.78-5.73		4.73		3.73-5.69		-0.090	-0.029

[1]Variables with a SMD > 0.1 in the pooled mRNA and J and J sample were included in PS weighting.
[2]Illustrates SMD prior to propensity weighting, to show differences between vaccinated and unvaccinated groups.
[3]SMD values after propensity weighting, SMD < 0.2 indicates no differences between groups, and that balance was achieved. Variables where balance was not achieved were included directly as covariates in the VE models.

[4]Other race include: Asian, Hawaiian or Other Pacific islander, American Indian or Alaskan Native, Other not-listed and multi-race.

G. COVID-19 VE Sensitivity Analysis: Propensity Score Estimation Using All Observations

Because the test-negative design has been interpreted as an indirect cohort and because COVID-19 is not currently a rare outcome, we also estimated propensity-for-vaccination scores using all study observations. In this sensitivity analysis, we conducted analyses using the same methods as described in the statistical analysis plan (Section C), with the exception that instead of using only the control group to estimate propensity scores, the entire study group was included to estimate propensity scores. Therefore, propensity scores for controls were not ascribed to cases as in the original study design. Balance among vaccinated and unvaccinated groups was achieved across all models for both ED/UC and hospitalization cohorts (Tables S34-37). Results show minimal differences in overall VE estimates for hospitalization, ICU, and ED/UC with this approach (Figures S21-23) compared to the main analysis (Figures 2-3). Minimal differences in VE estimates were also seen by race, ethnicity, age groups, and chronic conditions in the ED/UC (Figure S23 vs Figure 3) as well as the hospitalization cohort (Figure S22 vs Figure 2). Of note, a difference of 8% in VE estimates for the Johnson and Johnson vaccine was revealed for ED/UC, while a difference of 4% is shown for hospitalizations. Moderna and Pfizer VE estimates differed minimally.

Table S34. Unweighted and weighted standardized mean differences (SMD) for variables included in PS model[1] for mRNA-specific VE estimates - Hospitalizations events

	Sample	Unvaccinated		Partially or Fully Vaccinated		Unweighted	Weighted
	N	N	(Row %)	N	(Row %)	SMD[2]	SMD[3]
A. Hospitalizations							
All hospitalizations	40845	20406	(50)	20439	(50)	-	-
Site Characteristics							
Site-region							
Columbia - site-region 1	3088	2181	(71)	907	(29)	0.24	-0.01
HealthPartners - site-region 1	965	381	(39)	584	(61)	0.07	0.01
HealthPartners - site-region 2	16	8	(50)	8	(50)	<0.001	0.00
Intermountain Healthcare - site-region 1	239	133	(56)	106	(44)	0.02	0.00
Intermountain Healthcare - site-region 2	234	101	(43)	133	(57)	0.02	0.00
Intermountain Healthcare - site-region 3	1406	654	(47)	752	(53)	0.03	0.00
Intermountain Healthcare - site-region 4	715	340	(48)	375	(52)	0.01	0.00
Intermountain Healthcare - site-region 5	66	34	(52)	32	(48)	0.00	0.00
Intermountain Healthcare - site-region 6	467	245	(52)	222	(48)	0.01	0.00
Intermountain Healthcare - site-region 7	73	37	(51)	36	(49)	0.00	-0.01
Intermountain Healthcare - site-region 8	623	373	(60)	250	(40)	0.05	0.00
Kaiser Permanente Northern California - site-region 1	687	223	(32)	464	(68)	0.09	0.00
Kaiser Permanente Northern California - site-region 2	502	211	(42)	291	(58)	0.04	0.01
Kaiser Permanente Northern California - site-region 3	3139	997	(32)	2142	(68)	0.21	0.01
Kaiser Permanente Northern California - site-region 4	5474	1262	(23)	4212	(77)	0.43	0.01
Kaiser Permanente Northern California - site-region 5	1596	338	(21)	1258	(79)	0.23	0.01
Kaiser Permanente Northern California - site-region 6	655	123	(19)	532	(81)	0.16	0.00
Kaiser Permanente Northern California - site-region 7	262	91	(35)	171	(65)	0.05	0.00
Kaiser Permanente Northern California - site-region 8	1119	314	(28)	805	(72)	0.15	-0.01
Kaiser Permanente Northwest - site-region 1	1330	624	(47)	706	(53)	0.02	0.00
Kaiser Permanente Northwest - site-region 2	388	204	(53)	184	(47)	0.01	-0.01
Kaiser Permanente Northwest - site-region 3	181	78	(43)	103	(57)	0.02	0.00

Regenstrief Institute - site-region 1	2767	1966	(	71	)	801	(	29	)	0.23	0.00
Regenstrief Institute - site-region 2	557	317	(	57	)	240	(	43	)	0.03	0.00
Regenstrief Institute - site-region 3	170	116	(	68	)	54	(	32	)	0.05	0.00
Regenstrief Institute - site-region 4	925	577	(	62	)	348	(	38	)	0.08	0.00
Regenstrief Institute - site-region 5	3708	2181	(	59	)	1527	(	41	)	0.11	0.00
Regenstrief Institute - site-region 6	1143	681	(	60	)	462	(	40	)	0.07	0.00
Regenstrief Institute - site-region 7	112	64	(	57	)	48	(	43	)	0.02	0.00
Regenstrief Institute - site-region 8	853	513	(	60	)	340	(	40	)	0.06	-0.01
Regenstrief Institute - site-region 9	765	371	(	48	)	394	(	52	)	0.01	-0.01
Regenstrief Institute - site-region 10	269	142	(	53	)	127	(	47	)	0.01	-0.01
Regenstrief Institute - site-region missing	1037	665	(	64	)	372	(	36	)	0.09	0.01
University of Colorado - site-region 1	1585	1153	(	73	)	432	(	27	)	0.18	0.00
University of Colorado - site-region 2	1927	1239	(	64	)	688	(	36	)	0.13	0.00
University of Colorado - site-region 3	1802	1469	(	82	)	333	(	18	)	0.27	0.00
Patient Characteristics											
Sex											
Male	19263	9695	(	50	)	9568	(	50	)	-	-
Female	21581	10710	(	50	)	10871	(	50	)	-	-
Race											
White	28566	13886	(	49	)	14680	(	51	)	0.08	0.01
Black	3817	2393	(	63	)	1424	(	37	)	0.16	-0.01
Other[4]	2815	913	(	32	)	1902	(	68	)	0.19	0.01
Unknown	5647	3214	(	57	)	2433	(	43	)	0.11	-0.01
Ethnicity											
Hispanic/Latinx Ethnicity	4487	2376	(	53	)	2111	(	47	)	0.04	0.00
Not Hispanic/Latinx Ethnicity	30609	15361	(	50	)	15248	(	50	)	0.02	0.00
Unknown	5749	2669	(	46	)	3080	(	54	)	0.06	0.00

Age, continuous (mean, std)	73.7	71.7	(	11	)	75.6	(	10	)	0.36	0.02
Setting Characteristics											
Admitting Hospital											
Community	10439	5942	(	57	)	4497	(	43	)	0.19	-0.02
Tertiary	29359	13791	(	47	)	15568	(	53	)	<0.001	0.02
Unknown	1047	673	(	64	)	374	(	36	)	<0.001	0.00
Urban-Rural Classification of Facility											
Large Central Metro/Large Fringe Metro	26242	12379	(	47	)	13863	(	53	)	0.15	0.00
Medium Metro/Small Metro	12785	6885	(	54	)	5900	(	46	)	0.11	0.00
Micropolitan/Non-Core	724	448	(	62	)	276	(	38	)	0.06	-0.01
Unknown	1094	694	(	63	)	400	(	37	)	0.09	0.00
Hospital Beds											
0-49 beds	1215	631	(	52	)	584	(	48	)	-	-
50-99 beds	2550	1127	(	44	)	1423	(	56	)	-	-
100-249 beds	14281	5952	(	42	)	8329	(	58	)	-	-
250+ beds	21752	12023	(	55	)	9729	(	45	)	-	-
Unknown	1047	673	(	64	)	374	(	36	)	-	-
Hospital Ownership											
Non-Profit	39170	19384	(	49	)	19786	(	51	)	-	-
For Profit / Other	1675	1022	(	61	)	653	(	39	)	-	-
Underlying medical conditions (more than one may apply)											
Chronic respiratory condition	26942	13018	(	48	)	13924	(	52	)	-	-
Chronic non-respiratory condition	37225	18089	(	49	)	19136	(	51	)	0.18	0.01
Asthma	6138	2290	(	37	)	3848	(	63	)	0.21	0.02
COPD	12427	6153	(	50	)	6274	(	50	)	0.01	0.01

Other Chronic Lung Disease	17316	9029	(	52	)	8287	(	48	)	0.08	-0.01
Heart Failure	12598	5764	(	46	)	6834	(	54	)	0.11	0.01
Ischemic Heart Disease	12938	5831	(	45	)	7107	(	55	)	0.13	0.01
Hypertension	26902	12429	(	46	)	14473	(	54	)	0.21	0.02
Other Heart Disease	21861	9993	(	46	)	11868	(	54	)	0.18	0.01
Stroke	1822	987	(	54	)	835	(	46	)	-	-
Other Cerebrovascular Disease	1931	959	(	50	)	972	(	50	)	-	-
Diabetes Type 1	234	107	(	46	)	127	(	54	)	-	-
Diabetes Type 2	13824	6590	(	48	)	7234	(	52	)	-	-
Diabetes due to underlying conditions or other specified diabetes	210	133	(	63	)	77	(	37	)	-	-
Other Metabolic Disease (excluding diabetes)	25801	11632	(	45	)	14169	(	55	)	0.26	0.02
Clinical Obesity	9214	4578	(	50	)	4636	(	50	)	-	-
Clinical Underweight	4512	2602	(	58	)	1906	(	42	)	-	-
Renal Disease	13397	5708	(	43	)	7689	(	57	)	0.21	0.02
Liver Disease	3936	1978	(	50	)	1958	(	50	)	-	-
Blood Disorder	3162	1496	(	47	)	1666	(	53	)	-	-
Immunosuppression	15453	7161	(	46	)	8292	(	54	)	0.11	0.01
Organ Transplant	598	273	(	46	)	325	(	54	)	-	-
Cancer	5895	2652	(	45	)	3243	(	55	)	0.08	0.02
Dementia	4312	2124	(	49	)	2188	(	51	)	-	-
Other Neurological/Musculoskeletal Disorder	13528	6595	(	49	)	6933	(	51	)	0.03	0.00
Down Syndrome	13	9	(	69	)	4	(	31	)	-	-
Time Considerations (Median, Q1-Q3)											
Epi-curve (days)	4/17	4/16	(	3/22-5/12	)	4/17	(	3/24-5/12	)	0.06	0.01
7-day Moving Average Percent Positivity (days)	4.2	5.1	(	3.4-6.6	)	3.2	(	1.3-5.1	)	0.63	-0.04

[1]Variables with a SMD > 0.1 were included in PS weighting.

[2]Illustrates SMD prior to propensity weighting, to show differences between vaccinated and unvaccinated groups.

[3]SMD values after propensity weighting, SMD < 0.1 indicates no differences between groups, and that balance was achieved.

[4]Other race include Asian, Hawaiian or Other Pacific islander, American Indian or Alaskan Native, Other not-listed and multi-race.

Table S35. Unweighted and weighted standardized mean differences (SMD) for variables included in PS model[1] for mRNA-specific VE estimates - Emergency department and urgent care medical events

	Unvaccinated		Partially or Fully Vaccinated		Unweighted	Weighted
	N	Row %	N	Row %	SMD[2]	SMD[3]
A. Emergency department and urgent care						
All emergency department and urgent care medical events	11812	56.1	9254	43.9		
Site Characteristics						
Site-region						
Intermountain Healthcare - site-region 1	278	46.9	315	53.1	0.064	0.006
Intermountain Healthcare - site-region 2	180	51.0	173	49.0	0.027	0.003
Intermountain Healthcare - site-region 3	1542	48.4	1643	51.6	0.131	0.008
Intermountain Healthcare - site-region 4	721	51.4	681	48.6	0.050	0.003
Intermountain Healthcare - site-region 5	165	54.6	137	45.4	0.007	0.001
Intermountain Healthcare - site-region 6	623	56.0	490	44.0	0.001	0.000
Intermountain Healthcare - site-region 7	159	57.2	119	42.8	-0.005	0.002
Intermountain Healthcare - site-region 8	944	60.9	607	39.1	-0.055	-0.006
Kaiser Permanente Northwest - site-region 1	915	43.1	1207	56.9	0.176	0.010
Kaiser Permanente Northwest - site-region 2	916	47.9	996	52.1	0.105	0.001
Kaiser Permanente Northwest - site-region 3	269	50.3	266	49.7	0.038	0.002
Regenstrief Institute - site-region 1	658	74.4	227	25.6	-0.155	-0.014
Regenstrief Institute - site-region 2	112	58.6	79	41.4	-0.010	-0.003
Regenstrief Institute - site-region 3	316	62.7	188	37.3	-0.042	-0.008
Regenstrief Institute - site-region 4	216	74.7	73	25.3	-0.089	-0.008
Regenstrief Institute - site-region 5	574	66.0	296	34.0	-0.083	-0.008
Regenstrief Institute - site-region 6	1455	63.3	844	36.7	-0.103	0.005
Regenstrief Institute - site-region 7	445	70.5	186	29.5	-0.103	-0.010
Regenstrief Institute - site-region 8	119	68.8	54	31.2	-0.047	-0.005
Regenstrief Institute - site-region 9	477	68.1	223	31.9	-0.091	0.000
Regenstrief Institute - site-region 10	233	59.6	158	40.4	-0.020	-0.003
Regenstrief Institute - site-region Missing	495	62.9	292	37.1	-0.055	0.000
Patient Characteristics						
Sex						
Female	6334	55.1	5155	44.9		
Male	5487	57.3	4099	42.7		
Race						
White	9334	54.3	7857	45.7	0.152	0.014

Black	604	(	73.8	)	214	(	26.2	)	-0.145	-0.012
Other[4]	391	(	54.0	)	333	(	46.0	)	0.016	0.003
Unknown	1483	(	63.6	)	850	(	36.4	)	-0.107	-0.012
Ethnicity										
Hispanic/Latinx Ethnicity	725	(	63.5	)	417	(	36.5	)	-0.072	-0.013
Not Hispanic/Latinx Ethnicity	9718	(	54.7	)	8044	(	45.3	)	0.128	0.017
Unknown	1369	(	63.3	)	793	(	36.7	)	-0.100	-0.011
Age, continuous (mean, std)	67.84	(	11.4	)	72.52	(	11.0	)	0.410	0.020
Setting Characteristics										
Urban-Rural Classification of Facility										
Large Central Metro/Large Fringe Metro	4974	(	53.8	)	4278	(	46.2	)	0.083	0.010
Medium Metro/Small Metro	4744	(	56.3	)	3676	(	43.7	)	-0.009	-0.001
Micropolitan/Non-Core	1420	(	63.7	)	808	(	36.3	)	-0.107	-0.012
Unknown	674	(	57.8	)	492	(	42.2	)	-0.017	-0.003
Underlying medical conditions (more than one may apply)										
Chronic respiratory condition	3832	(	53.2	)	3372	(	46.8	)	0.084	-0.008
Chronic non-respiratory condition	6483	(	52.3	)	5922	(	47.7	)	0.185	0.002
Asthma	667	(	47.8	)	728	(	52.2	)	0.089	0.008
COPD	1968	(	55.5	)	1580	(	44.5	)	0.011	-0.002
Other Chronic Lung Disease	1939	(	50.8	)	1879	(	49.2	)		
Heart Failure	1509	(	49.7	)	1528	(	50.3	)	0.106	0.000
Ischemic Heart Disease	1461	(	49.3	)	1504	(	50.7	)	0.112	-0.004
Hypertension	3869	(	50.2	)	3831	(	49.8	)	0.179	0.010
Other Heart Disease	2802	(	49.4	)	2865	(	50.6	)	0.163	0.008
Stroke	210	(	46.8	)	239	(	53.2	)	0.056	0.005
Other CD	165	(	49.5	)	168	(	50.5	)		
Type 1 Diabetes	35	(	36.8	)	60	(	63.2	)		
Type 2 Diabetes	2042	(	51.4	)	1932	(	48.6	)	0.092	0.004
Other Diabetes	24	(	45.3	)	29	(	54.7	)		
Other Metabolic Disease (excluding diabetes)	2926	(	49.3	)	3007	(	50.7	)	0.172	0.015
Clinical Obesity	1203	(	51.3	)	1140	(	48.7	)		
Clinical Underweight	409	(	55.4	)	329	(	44.6	)		
Renal Disease	1522	(	45.9	)	1795	(	54.1	)	0.179	0.017
Liver	463	(	54.7	)	383	(	45.3	)	0.011	-0.005
Blood	342	(	46.2	)	398	(	53.8	)		
Immunosuppression	2017	(	48.6	)	2130	(	51.4	)	0.149	0.016
Organ Transplant	62	(	46.6	)	71	(	53.4	)		

Cancer	533	(	50.0	)	532	(	50.0	)	0.056	0.005
Dementia	443	(	42.8	)	591	(	57.2	)	0.122	0.012
Other Neurological/Musculoskeletal Disorder	1637	(	49.3	)	1685	(	50.7	)	0.119	0.005
Down Syndrome	2	(	50.0	)	2	(	50.0	)		
Time Considerations (Median, Q1-Q3)										
Epi-curve (days)	4/13		3/16-5/13		4/25		3/30-5/18		0.299	0.040
7-day Moving Average Percent Positivity (days)	4.96		3.86-6.38		4.6		3.65-5.62		-0.273	-0.031

[1]Variables with a SMD > 0.1 in the pooled mRNA and J and J sample were included in PS weighting.

[2]Illustrates SMD prior to propensity weighting, to show differences between vaccinated and unvaccinated groups.

[3]SMD values after propensity weighting, SMD < 0.2 indicates no differences between groups, and that balance was achieved. Variables where balance was not achieved were included directly as covariates in the VE models.

[4]Other race include Asian, Hawaiian or Other Pacific islander, American Indian or Alaskan Native, Other not-listed and multi-race.

Table S36. Unweighted and weighted standardized mean differences (SMD) for variables included in PS model[1] for unvaccinated and J&J vaccinees only - Hospitalization events

	Unvaccinated		Fully Vaccinated		Unweighted	Weighted
	N	Row %	N	Row %	SMD[2]	SMD[3]
A. Hospitalizations						
All Hospitalization events	10761	0.94	707	0.06		
Site Characteristics						
Site-region						
Columbia University - site-region 1	1141	0.97	38	0.03	0.20	0.00
Intermountain Healthcare - site-region 1	87	0.91	9	0.09	0.05	-0.01
Intermountain Healthcare - site-regions 2, 3	499	0.94	32	0.06	0.01	0.02
Intermountain Healthcare - site-region 4	220	0.97	6	0.03	0.10	-0.07
Intermountain Healthcare - site-region 5	23	0.96	1	0.04	0.02	-0.02
Intermountain Healthcare - site-region 6	171	0.93	12	0.07	0.01	-0.02
Intermountain Healthcare - site-regions 7, 8	218	0.89	27	0.11	0.11	0.00
Kaiser Permanente Northern California - site-region 1	198	0.92	18	0.08	0.05	0.01
Kaiser Permanente Northern California - site-region 2	173	0.96	8	0.04	0.04	0.00
Kaiser Permanente Northern California - site-region 3	850	0.93	61	0.07	0.03	0.01
Kaiser Permanente Northern California - site-region 4	1059	0.85	186	0.15	0.44	0.02
Kaiser Permanente Northern California - site-region 5	283	0.82	64	0.18	0.28	0.00
Kaiser Permanente Northern California - site-region 6	103	0.83	21	0.17	0.15	0.02
Kaiser Permanente Northern California - site-region 7	79	0.94	5	0.06	0.00	-0.02
Kaiser Permanente Northern California - site-region 8	267	0.91	27	0.09	0.08	-0.02
Kaiser Permanente Northwest - site-region 1	409	0.90	46	0.10	0.12	-0.02
Kaiser Permanente Northwest - site-region 2	80	0.93	6	0.07	0.01	-0.01
Kaiser Permanente Northwest - site-region 3, 4, 5	52	0.98	1	0.02	0.06	-0.01
Regenstrief Institute - site-regions 1,2,3	1593	0.98	38	0.02	0.32	-0.01
Regenstrief Institute - site-region 4	346	0.97	9	0.03	0.13	0.01
Regenstrief Institute - site-region 5	1282	0.97	46	0.03	0.19	0.08
Regenstrief Institute - site-regions 6,9	628	0.97	21	0.03	0.14	0.02
Regenstrief Institute - site-regions 7,8,10	423	0.98	7	0.02	0.19	-0.06
Regenstrief Institute - site-region missing	402	0.98	10	0.02	0.15	-0.06
Patient Characteristics						
Sex					-	-
Female	5685	0.94	388	0.06		
Male	5076	0.95	319	0.05		

Race									
White	6869	(	0.94	)	453	(	0.06	)	0.01	-0.02
Black	1445	(	0.94	)	85	(	0.06	)	0.04	0.05
Other[4]	573	(	0.88	)	77	(	0.12	)	0.21	0.01
Unknown	1874	(	0.95	)	92	(	0.05	)	0.12	-0.03
Ethnicity									
Hispanic/Latinx Ethnicity	1267	(	0.94	)	87	(	0.06	)	0.02	-0.03
Not Hispanic/Latinx Ethnicity	7554	(	0.94	)	460	(	0.06	)	0.11	-0.01
Unknown	1940	(	0.92	)	160	(	0.08	)	0.12	0.04
Age, continuous (mean, std)	69.4	(	11.5	)	69.5	(	11.7	)	0.01	-0.05
Setting Characteristics									
Urban-Rural Classification of Facility									
Large Central Metro/Large Fringe Metro	7158	(	0.93	)	522	(	0.07	)	0.16	0.08
Medium Metro/Small Metro	2900	(	0.64	)	1644	(	0.36	)	0.09	-0.06
Micropolitan/Non-Core	282	(	0.97	)	9	(	0.03	)	0.10	-0.01
Unknown	421	(	0.97	)	12	(	0.03	)	0.13	-0.06
Underlying medical conditions (more than one may apply)									
Chronic respiratory condition	6824	(	0.93	)	481	(	0.07	)		
Chronic non-respiratory condition	9249	(	0.93	)	674	(	0.07	)	0.33	0.09
Time Considerations (Median, Q1-Q3)									
Epi-curve (days)	4/30		4/12-5/19		05/01		4/15-5/20		0.06	0.04
7-day Moving Average Percent Positivity (%)	4.4		2.6-5.8		2.3		1.1-4.7		0.61	-0.06

[1]Variables with a SMD > 0.1 in the pooled mRNA and J and J sample were included in PS weighting.

[2]Illustrates SMD prior to propensity weighting, to show differences between vaccinated and unvaccinated groups.

[3]SMD values after propensity weighting, SMD < 0.2 indicates no differences between groups, and that balance was achieved. Variables where balance was not achieved were included directly as covariates in the VE models.

[4]Other race include Asian, Hawaiian or Other Pacific islander, American Indian or Alaskan Native, Other not-listed and multi-race.

Table S37. Unweighted and weighted standardized mean differences (SMD) for variables included in PS model[1] for unvaccinated and J&J vaccinees only - Emergency department and urgent care medical events

	Unvaccinated		Fully Vaccinated		Unweighted	Weighted
	N	Row %	N	Row %	SMD[2]	SMD[3]
A. Emergency department and urgent care						
All emergency department and urgent care medical events	8461	94.9	456	5.1		
Site Characteristics						
Site-region						
Intermountain Healthcare - site-region 1	227	95.0	12	5.0	-0.003	-0.001
Intermountain Healthcare - site-region 2	1278	93.8	84	6.2	0.092	0.016
Intermountain Healthcare - site-region 4	519	97.0	16	3.0	-0.111	0.000
Intermountain Healthcare - site-region 5	118	93.7	8	6.3	0.030	0.014
Intermountain Healthcare - site-region 6	493	93.7	33	6.3	0.060	-0.022
Intermountain Healthcare - site-region 7	717	91.9	63	8.1	0.189	0.032
Kaiser Permanente Northwest - site-region 1	741	90.8	75	9.2	0.267	-0.004
Kaiser Permanente Northwest - site-region 2	493	94.8	27	5.2	0.004	0.034
Kaiser Permanente Northwest - site-region 3	224	95.3	11	4.7	-0.015	0.028
Regenstrief Institute - site-region 1	891	97.3	25	2.7	-0.166	-0.037
Regenstrief Institute - site-region 4	404	96.7	14	3.3	-0.081	0.021
Regenstrief Institute - site-region 5	1044	96.3	40	3.7	-0.109	0.046
Regenstrief Institute - site-region 6	475	96.9	15	3.1	-0.102	-0.075
Regenstrief Institute - site-region 7	454	97.0	14	3.0	-0.103	-0.047
Regenstrief Institute - site-region missing	383	95.3	19	4.7	-0.017	-0.016
Patient Characteristics						
Sex						
Female	4554	94.6	260	5.4		
Male						
Race						
White	6542	94.6	373	5.4	0.107	0.040
Black	502	97.3	14	2.7	-0.123	-0.033
Other[4]	302	94.7	17	5.3	0.009	-0.050
Unknown	1115	95.5	52	4.5	-0.053	0.001
Ethnicity						
Hispanic/Latinx Ethnicity	586	95.4	28	4.6	-0.031	-0.012

Not Hispanic/Latinx Ethnicity	6849	(	94.7	)	380	(	5.3	)	0.061	-0.002
Unknown	1026	(	95.5	)	48	(	4.5	)	-0.049	0.012
Age, continuous (mean, std)	64.77	(	10.8	)	65.57	(	10.7	)	0.074	-0.030
Setting Characteristics										
Urban-Rural Classification of Facility										
Large Central Metro/Large Fringe Metro	3611	(	94.5	)	209	(	5.5	)	0.064	-0.003
Medium Metro/Small Metro	3333	(	95.1	)	170	(	4.9	)	-0.043	0.010
Micropolitan/Non-Core	987	(	95.5	)	46	(	4.5	)	-0.049	-0.005
Unknown	530	(	94.5	)	31	(	5.5	)	0.022	-0.006
Underlying medical conditions (more than one may apply)										
Chronic respiratory condition	2654	(	93.7	)	179	(	6.3	)	0.169	0.029
Chronic non-respiratory condition	4382	(	94.4	)	258	(	5.6	)	0.096	0.013
Time Considerations (Median, Q1-Q3)										
Epi-curve (days)	4/30		4/9-5/21		5/11		4/22-5/27		0.361	0.065
7-day Moving Average Percent Positivity (%)	4.85		3.87-5.88		4.72		3.73-5.69		-0.157	-0.017

[1]Variables with a SMD > 0.1 in the pooled mRNA and J and J sample were included in PS weighting.

[2]Illustrates SMD prior to propensity weighting, to show differences between vaccinated and unvaccinated groups.

[3]SMD values after propensity weighting, SMD < 0.2 indicates no differences between groups, and that balance was achieved. Variables where balance was not achieved were included directly as covariates in the VE models.

[4]Other race include Asian, Hawaiian or Other Pacific islander, American Indian or Alaskan Native, Other not-listed and multi-race.

Figure S21. Estimates of COVID-19 vaccine effectiveness (VE) among COVID-19 associated hospitalizations and emergency department or urgent care (ED/UC) encounters by vaccine product

Subgroup	Total	SARS-CoV-2 Positive	Row %	Adjusted VE % (CI)
VE against COVID-19 hospitalizations				
BNT162b2 (Pfizer-BioNTech)				
Unvaccinated (Referent)	20406	3695	18.1	
Partial 1-Dose mRNA Vaccinated	1444	140	9.7	38 (24-50)
Partial 2-Dose mRNA Vaccinated	1348	57	4.2	74 (65-81)
Full 2-dose mRNA Vaccinated	8500	163	1.9	87 (84-89)
mRNA-1273 (Moderna)				
Unvaccinated (Referent)	20406	3695	18.1	
Partial 1-Dose mRNA Vaccinated	1639	91	5.6	72 (63-78)
Partial 2-Dose mRNA Vaccinated	1134	50	4.4	73 (62-81)
Full 2-dose mRNA Vaccinated	6374	95	1.5	92 (90-93)
Ad26.COV2.S (Johnson & Johnson)				
Unvaccinated (Referent)	20406	3695	18.1	
Full 1-dose Vaccinated	707	30	4.2	71 (55-81)
VE against COVID-19 ICU Admissions				
BNT162b2 or mRNA-1273				
Unvaccinated (Referent)	4024	692	17.2	
Partial 1-Dose mRNA Vaccinated	512	39	7.6	60 (41-72)
Partial 2-Dose mRNA Vaccinated	388	15	3.9	78 (61-87)
Full 2-dose mRNA Vaccinated	2359	38	1.6	90 (85-93)
VE against COVID-19 ED/UC				
BNT162b2 (Pfizer-BioNTech)				
Unvaccinated (Referent)	11812	2847	24.1	
Partial 1-Dose mRNA Vaccinated	912	88	9.6	60 (48-70)
Partial 2-Dose mRNA Vaccinated	711	31	4.4	84 (75-89)
Full 2-dose mRNA Vaccinated	3589	105	2.9	89 (86-92)
mRNA-1273 (Moderna)				
Unvaccinated (Referent)	11812	2847	24.1	
Partial 1-Dose mRNA Vaccinated	1008	67	6.6	74 (66-80)
Partial 2-Dose mRNA Vaccinated	558	35	6.3	75 (63-83)
Full 2-dose mRNA Vaccinated	2476	49	2.0	93 (91-95)
Ad26.COV2.S (Johnson & Johnson)				
Unvaccinated (Referent)	8461	2200	26.0	
Full 1-dose Vaccinated	456	29	6.4	81 (70-88)

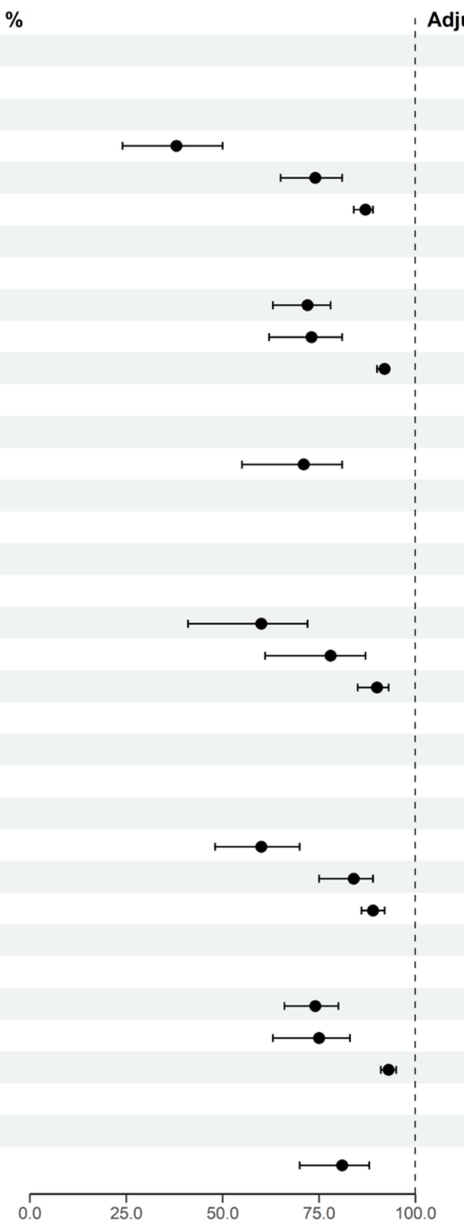


Figure S22. Estimated vaccine effectiveness (VE) of full 2-dose vaccination with messenger RNA (mRNA) vaccines among COVID-19 associated hospitalizations by age group, race, ethnicity, and underlying medical conditions

Subgroup	Total	SARS-CoV-2 Positive	Row %	VE % (CI)
mRNA VE against COVID-19 hospitalizations				
VE both mRNA vaccines aged ≥50 years				
Unvaccinated (Referent)	20406	3695	18.1	
Partial 1-Dose mRNA Vaccinated	3083	231	7.5	54 (46-61)
Partial 2-Dose mRNA Vaccinated	2482	107	4.3	72 (65-78)
Full 2-dose mRNA Vaccinated	14874	258	1.7	88 (86-90)
VE COVID-19 vaccines (aged ≥85 years)				
Unvaccinated (Referent)	2960	447	15.1	
Partial 1-Dose mRNA Vaccinated	549	41	7.5	37 (9-56)
Partial 2-Dose mRNA Vaccinated	448	27	6.0	54 (29-70)
Full 2-dose mRNA Vaccinated	3306	68	2.1	83 (78-87)
VE COVID-19 vaccines among aged ≥50 years with ≥1 chronic respiratory condition				
Unvaccinated (Referent)	13018	2359	18.1	
Partial 1-Dose mRNA Vaccinated	2033	140	6.9	55 (45-63)
Partial 2-Dose mRNA Vaccinated	1634	62	3.8	75 (67-82)
Full 2-dose mRNA Vaccinated	10257	152	1.5	89 (86-91)
VE COVID-19 vaccines among aged ≥50 years with ≥1 chronic non-respiratory condition				
Unvaccinated (Referent)	18089	3043	16.8	
Partial 1-Dose mRNA Vaccinated	2835	201	7.1	53 (45-60)
Partial 2-Dose mRNA Vaccinated	2302	97	4.2	72 (64-78)
Full 2-dose mRNA Vaccinated	13999	240	1.7	87 (85-89)
VE COVID-19 vaccines among Black adults aged ≥50 years				
Unvaccinated (Referent)	2393	36	1.5	
Partial 1-Dose mRNA Vaccinated	269	21	7.8	55 (26-73)
Partial 2-Dose mRNA Vaccinated	194	7	3.6	80 (52-91)
Full 2-dose mRNA Vaccinated	961	20	2.1	86 (76-92)
VE COVID-19 vaccines among Hispanic adults aged ≥50 years				
Unvaccinated (Referent)	2376	656	27.6	
Partial 1-Dose mRNA Vaccinated	307	36	11.7	56 (34-71)
Partial 2-Dose mRNA Vaccinated	264	16	6.1	78 (58-88)
Full 2-dose mRNA Vaccinated	1540	35	2.3	88 (82-92)
mRNA VE against COVID-19 ICU admission				
VE both mRNA vaccines aged ≥50 years				
Unvaccinated (Referent)	4024	692	17.2	
Partial 1-Dose mRNA Vaccinated	512	39	7.6	60 (41-72)
Partial 2-Dose mRNA Vaccinated	388	15	3.9	78 (61-87)
Full 2-dose mRNA Vaccinated	2359	38	1.6	90 (85-93)

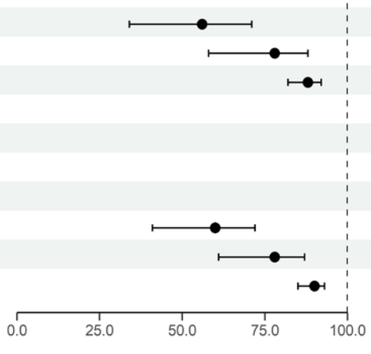


Figure S23. Estimated vaccine effectiveness (VE) of full 2-dose vaccination with messenger RNA (mRNA) vaccines among COVID-19 associated emergency department or urgent care (ED/UC) encounters by age group, race, ethnicity, and underlying medical conditions.

Subgroup	Total	SARS-CoV-2 Positive	Row %	VE % (CI)
mRNA VE among COVID-19 ED/UC medical events				
VE both mRNA vaccines aged ≥50 years				
Unvaccinated (Referent)	11812	2847	24.1	
Partial 1-Dose mRNA Vaccinated	1920	155	8.1	68 (61-73)
Partial 2-Dose mRNA Vaccinated	1269	66	5.2	80 (74-85)
Full 2-dose mRNA Vaccinated	6065	154	2.5	91 (89-93)
VE COVID-19 vaccines (aged ≥85 years)				
Unvaccinated (Referent)	1027	143	13.9	
Partial 1-Dose mRNA Vaccinated	223	13	5.8	54 (11-76)
Partial 2-Dose mRNA Vaccinated	172	10	5.8	59 (17-80)
Full 2-dose mRNA Vaccinated	921	20	2.2	83 (72-90)
VE COVID-19 vaccines among aged ≥50 years with ≥1 chronic respiratory condition				
Unvaccinated (Referent)	3832	677	17.7	
Partial 1-Dose mRNA Vaccinated	703	36	5.1	71 (59-80)
Partial 2-Dose mRNA Vaccinated	463	20	4.3	78 (63-86)
Full 2-dose mRNA Vaccinated	2206	44	2.0	91 (87-93)
VE COVID-19 vaccines among aged ≥50 years with ≥1 chronic non-respiratory condition				
Unvaccinated (Referent)	6483	1293	19.9	
Partial 1-Dose mRNA Vaccinated	1179	67	5.7	73 (65-80)
Partial 2-Dose mRNA Vaccinated	796	33	4.1	80 (70-86)
Full 2-dose mRNA Vaccinated	3947	98	2.5	90 (87-92)
VE COVID-19 vaccines among Black adults aged ≥50 years				
Unvaccinated (Referent)	604	166	27.5	
Partial 1-Dose mRNA Vaccinated	55	7	12.7	64 (14-85)
Partial 2-Dose mRNA Vaccinated	25	1	4.0	94 (47-99)
Full 2-dose mRNA Vaccinated	134	3	2.2	96 (87-99)
VE COVID-19 vaccines among Hispanic adults aged ≥50 years				
Unvaccinated (Referent)	725	248	34.2	
Partial 1-Dose mRNA Vaccinated	102	14	13.7	70 (43-84)
Partial 2-Dose mRNA Vaccinated	65	5	7.7	86 (63-94)
Full 2-dose mRNA Vaccinated	250	23	9.2	85 (76-91)