Supplemental Online Content

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

I. Supplementary Appendix A. Investigators and Collaborators

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II. Supplementary Appendix B. Supplementary Tables and Figures

Supplementary Table 1. Modified WHO COVID-19 Clinical Progression Scale used in this analysis to assess disease severity among adults hospitalized with COVID-19.

Patient State	Descriptor	Severity Level
Uninfected	Uninfected; no viral RNA detected	0 [not evaluated in this analysis]
Ambulatory mild disease	Asymptomatic; viral RNA detected	1 [not evaluated in this analysis]
	Symptomatic; independent	2 [not evaluated in this analysis]
	Symptomatic; assistance needed	3 [not evaluated in this analysis]
Hospitalized: moderate disease	Hospitalized; no oxygen therapy	4
	Hospitalized; standard oxygen therapy by mask or nasal prongs	5
Hospitalized: severe disease	Hospitalized, oxygen by high flow nasal cannula or non-invasive ventilation	6
	Invasive mechanical ventilation	7
	Invasive mechanical ventilation plus other organ support including ECMO, vasopressors or new renal replacement therapy	8
Death	Death	9

Abbreviations: ECMO = extracorporeal membrane oxygenation; RNA = ribonucleic acid; WHO = world health organization

[a] Uninfected and mild severity were not included as the sample was restricted to hospitalized, laboratory-confirmed COVID-19 cases.

Supplementary Table 2. Underlying medical conditions obtained through medical record review. Condition categories included cardiovascular disease, neurologic disease, pulmonary disease, gastrointestinal disease, endocrine disease, renal disease, hematologic disease, malignancy, immunosuppression not captured in other categories, autoimmune condition, other condition (sarcoidosis, amyloidosis, unintentional weight loss ≥10 pounds in the last 90 days). All conditions considered as immunocompromising are noted (*).

Cardiovascular disease
Heart failure
Peripheral vascular disease that limits mobility
Prior myocardial infarction
Cardiac arrhythmias including atrial fibrillation and ventricular arrhythmias
Valvular heart disease
Hypertension
Neurologic disease
Dementia
Prior stroke
Prior transient ischemic attack (TIA, “mini-stroke”)
Brain or spinal cord injury with loss of limb function
Cerebral palsy
Muscular dystrophy
Multiple sclerosis
Myasthenia gravis
Anterolateral sclerosis (ALS)
Pulmonary disease
Asthma
Chronic obstructive pulmonary disease
Cystic fibrosis
Pulmonary fibrosis
Pulmonary hypertension
Home oxygen use (except at night for sleep disorder)
Tracheostomy
Home non-invasive ventilation use (except at night for sleep disorder)
Home invasive ventilation use
Gastrointestinal disease
Feeding through a tube
Inflammatory bowel disease including Crohn's Disease or Ulcerative Colitis*
Cirrhosis (clinical diagnosis of cirrhosis)
Chronic liver disease without cirrhosis
Peptic ulcer disease
Endocrine disease
Diabetes mellitus without end organ damage
Diabetes mellitus with end organ damage
Adrenal insufficiency
Hypothyroidism
Renal disease
Chronic kidney disease without chronic renal replacement therapy
End stage renal disease on chronic renal replacement therapy (including hemodialysis or peritoneal dialysis)
Prior kidney transplant*
Hematologic disease

Sickle cell disease (all variants)
Prior stem cell or bone marrow transplant*
Coagulopathy or other bleeding disorder, such as hemophilia
Chronic anemia
Thalassemia
Cancer/Malignancy
Active solid organ cancer without metastases; active cancer defined as treatment for the cancer or newly diagnosed cancer in the past 6 months*
Active solid organ cancer with metastases; active cancer defined as treatment for the cancer or newly diagnosed cancer in the past 6 months*
Active hematologic cancer (such as leukemia/lymphoma/myeloma) or active cancer defined as treatment for the cancer or newly diagnosed cancer in the past 6 months*
Other immunosuppression
Human Immunodeficiency Virus (HIV) infection without AIDS*
AIDS*
Congenital immunodeficiency disorder*
Prior splenectomy*
Prior solid organ transplant*
Immunosuppression medication*
Other immunosuppression condition
Autoimmune
Systemic Lupus Erythematosus*
Rheumatoid arthritis*
Psoriasis*
Scleroderma*
Other autoimmune disease
Other
Unintentional weight loss of at least 10 pounds in past 90 days
Sarcoidosis
Amyloidosis

Supplementary Table 3. Association between hospitalization for COVID-19 and prior receipt of full vaccination with a two-dose series of a mRNA vaccine, restricted to patients without immunocompromising conditions.

Subgroup	Vaccinated Case Patients / Total Case Patients (%)	Vaccinated Control Patients / Total Control Patients (%)	Absolute Difference (95% CI), %	Adjusted Odds Ratio (95% CI)[a]
Overall	186/1662 (11.2)	1039/1942 (53.5)	-42.3 (-45.0 to -39.6)	0.10 (0.09 to 0.13)
By age group				
18-49	29/674 (4.3)	162/546 (29.7)	-25.4 (-29.5 to -21.2)	0.09 (0.06 to 0.14)
50-64	42/528 (8.0)	276/558 (49.5)	-41.5 (-46.3 to -36.8)	0.08 (0.06 to 0.12)
≥65	115/460 (25.0)	601/838 (71.7)	-46.7 (-51.7 to -41.7)	0.12 (0.09 to 0.16)
By time between vaccine dose #2 and illness onset				
14-120 days	102/1578 (6.5)	840/1743 (48.2)	-41.7 (-44.4 to -39.1)	0.09 (0.07 to 0.11)
>120 days	84/1560 (5.4)	199/1102 (18.1)	-12.7 (-15.2 to -10.1)	0.17 (0.12 to 0.24)
By month of illness onset overall and by time between vaccine dose #2 and illness onset				
March-June 2021 overall (Alpha period)	70/934 (7.5)	669/1330 (50.3)	-42.8 (-46.0 to -39.6)	0.10 (0.07 to 0.13)
14-120 days since vaccination	66/930 (7.1)	627/1288 (48.7)	-41.6 (-44.8 to -38.4)	0.10 (0.07 to 0.13)
>120 days since vaccination	4/868 (0.5)	42/703 (6.0)	-5.5 (-7.3 to -3.7)	0.09 (0.03 to 0.27)
July-August 2021 overall (Delta period)	116/728 (15.9)	370/612 (60.5)	-44.5 (-49.2 to -39.8)	0.11 (0.08 to 0.15)
14-120 days since vaccination	36/648 (5.6)	213/455 (46.8)	-41.3 (-46.2 to -36.3)	0.07 (0.04 to 0.10)
>120 days since vaccination	80/692 (11.6)	157/399 (39.3)	-27.8 (-33.1 to -22.4)	0.17 (0.12 to 0.25)
By SARS-CoV-2 lineage[b]				
Alpha (B.1.1.7)	5/194 (2.6)	669/1330 (50.3)	-47.7 (-51.2 to -44.2)	0.03 (0.01 to 0.07)
Delta (B.1617.2 or AY)	39/239 (16.3)	370/612 (60.5)	-44.1 (-50.2 to -38.1)	0.10 (0.07 to 0.16)
By vaccine product overall and by time between vaccine dose #2 and illness onset				
Pfizer-BioNTech overall	133/1609 (8.3)	614/1517 (40.5)	-32.2 (-35.0 to -29.4)	0.13 (0.10 to 0.17)
14-120 days since vaccination	67/1543 (4.3)	496/1399 (35.5)	-31.1 (-33.8 to -28.4)	0.10 (0.07 to 0.13)
>120 days since vaccination	66/1542 (4.3)	118/1021 (11.6)	-7.3 (-9.5 to -5.1)	0.24 (0.17 to 0.35)
Moderna overall	53/1529 (3.5)	425/1328 (32.0)	-28.5 (-31.2 to -25.9)	0.07 (0.05 to 0.10)
14-120 days since vaccination	35/1511 (2.3)	344/1247 (27.6)	-25.3 (-27.9 to -22.7)	0.07 (0.05 to 0.10)

Subgroup	Vaccinated Case Patients / Total Case Patients (%)	Vaccinated Control Patients / Total Control Patients (%)	Absolute Difference (95% CI), %	Adjusted Odds Ratio (95% CI)[a]
>120 days since vaccination	18/1494 (1.2)	81/984 (8.2)	-7.0 (-8.8 to -5.2)	0.08 (0.05 to 0.15)

Abbreviations: CI = confidence interval; OR = odds ratio

[a] Models were mixed-effects logistic regression models with vaccination status (fully vaccinated vs unvaccinated) as the primary independent variable, case/control status (hospitalized with COVID-19 vs hospitalized without COVID-19) as the dependent variable, enrolling site as a random effect, and the following co-variables: admission date (biweekly intervals), age group (18-49, 50-64, ≥65 years), sex, and self-reported race/ethnicity. Models stratified by age group were adjusted for continuous age in years.

[b] Alpha estimates restricted to March-June illness onset dates (Alpha period); Delta estimates restricted to July-August illness onset dates (Delta period).

Supplementary Table 4. Association between hospitalization for COVID-19 and prior receipt of full vaccination with a two-dose series of a mRNA vaccine, restricted to patients without immunocompromising conditions and aged 18-64 years.

Subgroup	Vaccinated Case Patients / Total Case Patients (%)	Vaccinated Control Patients / Total Control Patients (%)	Absolute Difference (95% CI), %	Adjusted Odds Ratio (95% CI)[a]
Overall	71/1202 (5.9)	438/1104 (39.7)	-33.8 (-36.9 to -30.6)	0.08 (0.06 to 0.11)
By time between vaccine dose #2 and illness onset				
14-120 days	49/1180 (4.2)	368/1034 (35.6)	-31.4 (-34.6 to -28.3)	0.08 (0.05 to 0.11)
>120 days	22/1153 (1.9)	70/736 (9.5)	-7.6 (-9.9 to -5.3)	0.12 (0.07 to 0.21)
By month of illness onset overall and by time between vaccine dose #2 and illness onset				
March-June 2021 overall (Alpha period)	28/698 (4.0)	262/755 (34.7)	-30.7 (-34.4 to -27.0)	0.09 (0.06 to 0.13)
14-120 days since vaccination	27/697 (3.9)	242/735 (32.9)	-29.1 (-32.7 to -25.4)	0.09 (0.06 to 0.14)
>120 days since vaccination	1/671 (0.1)	20/513 (3.9)	-3.7 (-5.4 to -2.0)	0.03 (0.004 to 0.30)
July-August 2021 overall (Delta period)	43/504 (8.5)	176/349 (50.4)	-41.9 (-47.7 to -36.1)	0.08 (0.05 to 0.12)
14-120 days since vaccination	22/483 (4.6)	126/299 (42.1)	-37.6 (-43.5 to -31.7)	0.06 (0.03 to 0.10)
>120 days since vaccination	21/482 (4.4)	50/223 (22.4)	-18.1 (-23.8 to -12.3)	0.13 (0.07 to 0.24)
By vaccine product overall and by time between vaccine dose #2 and illness onset				
Pfizer-BioNTech overall	54/1185 (4.6)	252/918 (27.5)	-22.9 (-26.0 to -19.8)	0.12 (0.08 to 0.16)
14-120 days since vaccination	36/1167 (3.1)	216/882 (24.5)	-21.4 (-24.4 to -18.4)	0.10 (0.06 to 0.14)
>120 days since vaccination	18/1149 (1.6)	36/702 (5.1)	-3.6 (-5.3 to -1.8)	0.21 (0.11 to 0.40)
Moderna overall	17/1148 (1.5)	186/852 (21.8)	-20.4 (-23.2 to -17.5)	0.04 (0.03 to 0.08)
14-120 days since vaccination	13/1144 (1.1)	152/818 (18.6)	-17.4 (-20.2 to -14.7)	0.05 (0.03 to 0.08)
>120 days since vaccination	4/1135 (0.4)	34/700 (4.9)	-4.5 (-6.1 to -2.9)	0.04 (0.01 to 0.12)

Abbreviations: CI = confidence interval; OR = odds ratio

[a] Models were mixed-effects logistic regression models with vaccination status (fully vaccinated vs unvaccinated) as the primary independent variable, case/control status (hospitalized with COVID-19 vs hospitalized without COVID-19) as the dependent variable, enrolling site as a random effect, and the following co-variables: admission date (biweekly intervals), continuous age in years, sex, and self-reported race/ethnicity.

Supplementary Table 5. Association between hospitalization for COVID-19 and prior receipt of full vaccination with a two-dose series of a mRNA vaccine, restricted to patients without immunocompromising conditions and aged ≥65 years.

Subgroup	Vaccinated Case Patients / Total Case Patients (%)	Vaccinated Control Patients / Total Control Patients (%)	Absolute Difference (95% CI), %	Adjusted Odds Ratio (95% CI)
Overall	115/460 (25.0)	601/838 (71.7)	-46.7 (-51.7 to -41.7)	0.12 (0.09 to 0.16)
By time between vaccine dose #2 and illness onset				
14-120 days	53/398 (13.3)	472/709 (66.6)	-53.3 (-58.1 to -48.4)	0.09 (0.06 to 0.13)
>120 days	62/407 (15.2)	129/366 (35.2)	-20.0 (-26.0 to -14.0)	0.21 (0.13 to 0.32)
By month of illness onset overall and by time between vaccine dose #2 and illness onset				
March-June 2021 overall (Alpha period)	42/236 (17.8)	407/575 (70.8)	-53.0 (-59.1 to -46.9)	0.10 (0.06 to 0.14)
14-120 days since vaccination	39/233 (16.7)	385/553 (69.2)	-52.9 (-59.0 to -46.7)	0.09 (0.06 to 0.14)
>120 days since vaccination	3/197 (1.5)	22/190 (11.6)	-10.1 (-14.9 to -5.2)	0.13 (0.03 to 0.50)
July-August 2021 overall (Delta period)	73/224 (32.6)	194/263 (73.8)	-41.2 (-49.3 to -33.1)	0.12 (0.07 to 0.20)
14-120 days since vaccination	14/165 (8.5)	87/156 (55.8)	-47.3 (-56.2 to -38.4)	0.07 (0.03 to 0.14)
>120 days since vaccination	59/210 (28.1)	107/176 (60.8)	-32.7 (-42.1 to -23.3)	0.17 (0.10 to 0.30)
By vaccine product overall and by time between vaccine dose #2 and illness onset				
Pfizer-BioNTech overall	79/424 (18.6)	362/599 (60.4)	-41.8 (-47.2 to -36.4)	0.14 (0.10 to 0.19)
14-120 days since vaccination	31/376 (8.2)	280/517 (54.2)	-45.9 (-51.0 to -40.8)	0.09 (0.06 to 0.14)
>120 days since vaccination	48/393 (12.2)	82/319 (25.7)	-13.5 (-19.3 to -7.7)	0.25 (0.15 to 0.40)
Moderna overall	36/381 (9.4)	239/476 (50.2)	-40.8 (-46.1 to -35.4)	0.10 (0.07 to 0.15)
14-120 days since vaccination	22/367 (6.0)	192/429 (44.8)	-38.8 (-44.1 to -33.5)	0.09 (0.05 to 0.14)
>120 days since vaccination	14/359 (3.9)	47/284 (16.5)	-12.6 (-17.4 to -7.9)	0.13 (0.07 to 0.27)

Abbreviations: CI = confidence interval; OR = odds ratio

[a] Models were mixed-effects logistic regression models with vaccination status (fully vaccinated vs unvaccinated) as the primary independent variable, case/control status (hospitalized with COVID-19 vs hospitalized without COVID-19) as the dependent variable, enrolling site as a random effect, and the following co-variables: admission date (biweekly intervals), continuous age in years, sex, and self-reported race/ethnicity.

Supplementary Table 6. Treatments, outcomes, and severity of illness among hospitalized COVID-19 cases by vaccination status.

Characteristic	Vaccine breakthrough cases (n=142)	Unvaccinated cases (n = 1055)	P-value[a]
Any of the following COVID-19-related treatments, No. / Total (%)[b]	77/117 (65.8)	862/1024 (84.2)	<.001
Corticosteroids	74/117 (63.2)	824/1024 (80.5)	<.001
Remdesivir	52/117 (44.4)	650/1024 (63.5)	<.001
Convalescent plasma	9/117 (7.7)	23/1024 (2.2)	.001
Tocilizumab	11/117 (9.4)	178/1024 (17.4)	.03
Baricitinib	0/117 (0.0)	7/1024 (0.7)	.37
Admitted to ICU, No. / Total (%)	35/142 (24.6)	423/1055 (40.1)	<.001
Any oxygen support, No. / Total (%)	98/142 (69.0)	889/1055 (84.3)	<.001
HFNC	21/142 (14.8)	365/1055 (34.6)	<.001
NIPPV	20/142 (14.1)	182/1055 (17.3)	.34
IMV	11/142 (7.7)	243/1055 (23.0)	<.001
ECMO	1/142 (0.7)	39/1055 (3.7)	.06
Venous thromboembolic event, No. / Total (%)[c]	7/142 (4.9)	64/1055 (6.1)	.59
Stroke, No. / Total (%)	0/142 (0.0)	22/1055 (2.1)	.08
Myocardial infarction, No. / Total (%)	2/142 (1.4)	21/1055 (2.0)	.64
Death within 28 days of admission, No. / Total (%)	9/142 (6.3)	91/1055 (8.6)	.36
Death or invasive mechanical ventilation, No. / Total (%)	17/142 (12.0)	261/1055 (24.7)	.001

Abbreviations: ECMO = extracorporeal membrane oxygenation; HFNC = high-flow nasal cannula; ICU = intensive care unit; IMV = invasive mechanical ventilation; NIPPV = nasal intermittent positive-pressure ventilation

[a] Chi-square test p-values presented.

[b] COVID-19 treatment data reported only for patients known by their treating clinicians to have COVID-19; this excluded patients with negative SARS-CoV-2 clinical testing who were enrolled as a test-negative control and later reclassified as a case based on positive SARS-CoV-2 research testing that was not available to clinicians.

[c] Deep vein thrombosis and/or pulmonary embolism.

Supplementary Table 7. Odds of prior mRNA COVID-19 vaccination among COVID-19 cases who received in-hospital COVID-19 therapeutics[a] and those who did not.

				Adjusted odds ratio of treatment (vaccinated versus unvaccinated)[b]	
	Fully vaccinated cases (n=117)	**Unvaccinated cases (n = 1024)**	**Absolute different (95% CI)**		
	No./Total (%)	**No./Total (%)**		**aOR**	**95% CI**
Received ≥1 COVID-19 therapeutic[c]					
Overall	77/117 (65.8)	862/1024 (84.2)	-18.4 (-27.2 to -9.5)	0.32	(0.20 to 0.52)
Without immunocompromising condition	30/63 (47.6)	740/883 (83.8)	-36.2 (-48.7 to -23.6)	0.19	(0.11 to 0.33)
With immunocompromising condition	47/54 (87.0)	122/141 (86.5)	0.5 (-10.1 to 11.1)	0.79	(0.28 to 2.26)
Age 18-64	32/51 (62.7)	672/791 (85.0)	-22.2 (-35.7 to -8.7)	0.24	(0.12 to 0.46)
Age ≥65	45/66 (68.2)	190/233 (81.5)	-13.4 (-25.6 to -1.1)	0.42	(0.21 to 0.85)

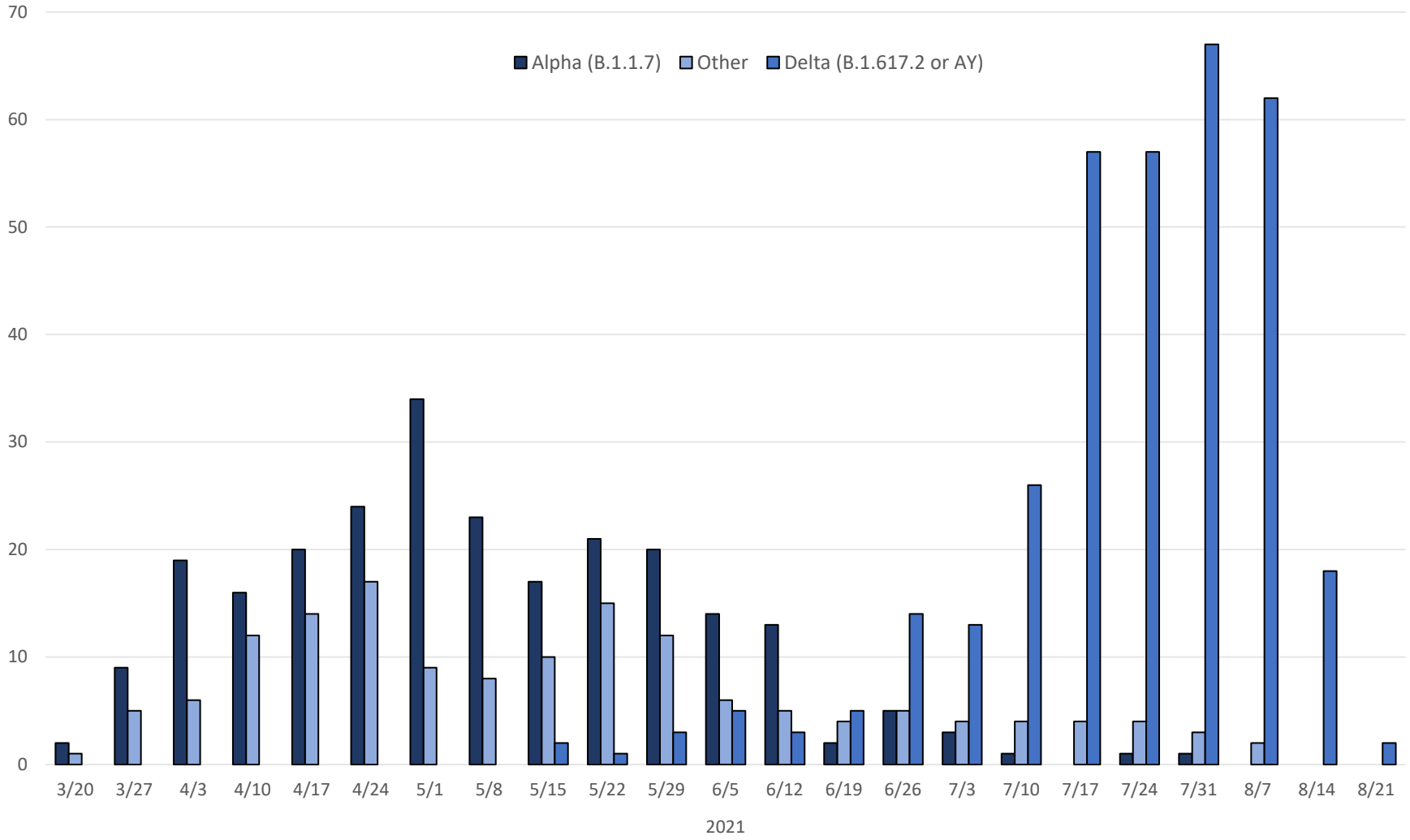
Abbreviation: aOR = adjusted odds ratio; CI = confidence interval

[a] Information on COVID-19 therapeutics was not collected on patients enrolled as test-negative controls who later had a positive research SARS-CoV-2 RT-PCR test; denominator therefore includes COVID-19 case patients enrolled as SARS-CoV-2 cases.

[b] Adjusted for age group (18-49, 50-64, ≥65 years), sex, race and ethnicity, number of underlying conditions by category (0, 1, 2, 3, ≥4).

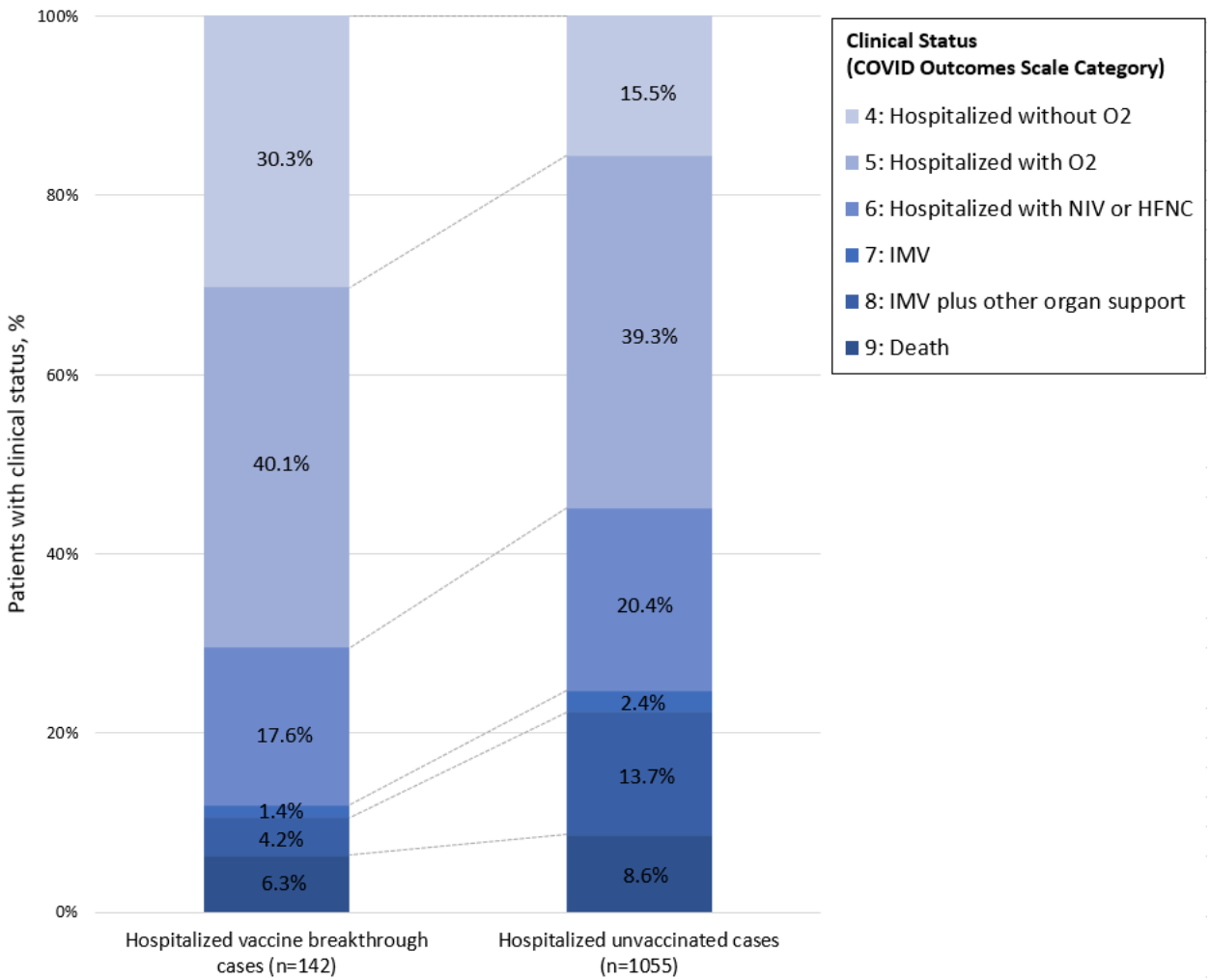
[c] COVID-19 therapeutic agents including systemic corticosteroids, remdesivir, convalescent plasma, tocilizumab, or baricitinib.

eFigure 1. Whole genome sequencing SARS-CoV-2 lineage determinationa among COVID-19 cases by admission week. The predominate variant changed from Alpha (B.1.1.7) to Delta (B1.617.2) in June 2021. The x-axis date represents the end date of the admission week. The y-axis represents the number of successfully sequenced SARS-CoV-2 viruses.



[a] SARS-CoV-2 lineages were assigned with >80% coverage using PANGOLIN. Viruses underwent whole genome sequencing if the cycle threshold value for at least one of 2 nucleocapsid gene targets was <32; 730/1983 (36.8%) cases were successfully sequenced. Other non-Alpha (B.1.1.7) and non-Delta (B.1.617.2 or AY) lineages sequenced included: Gamma/P.1 (44), B.1.526 (14), B.1.526.1 (12), B.1.429 (11), B.1.621 (11), B.1 (10), B.1.1.519 (7), B.1.2 (6), Beta B.1.351 (6), B.1.526.3 (4), B.1.1.28 (3), B.1.526.2 (3), C.37 (3), B.1.525 (2), B.1.621.1 (2), B.1.623 (2), B.1.628 (2), B.1.1.318 (1), B.1.1.372 (1), B.1.1.361 (1), B.1.441 (1), B.1.517 (1), B.1.612 (1), C.36.3 (1), R.1 (1).

eFigure 2. Highest severity level experienced on the WHO COVID-19 Clinical Progression Scale during the first 28 days of hospitalization among vaccine breakthrough COVID-19 cases and unvaccinated COVID-19 cases. Overall, the severity level was lower in vaccinated breakthrough cases than unvaccinated cases (adjusted odds ratio[a]: 0.36; 95% CI: 0.25—0.51).



Clinical status (COVID Outcomes Scale category)	Vaccine breakthrough cases (n=142)	Unvaccinated cases (n=1053)
4: Hospitalized; no oxygen therapy	43 (30.3%)	164 (15.5%)
5: Hospitalized; standard oxygen therapy by mask or nasal prongs	57 (40.1%)	415 (39.3%)
6: Hospitalized, oxygen by high flow nasal cannula or non-invasive ventilation	25 (17.6%)	215 (20.4%)
7: Invasive mechanical ventilation	2 (1.4%)	25 (2.4%)
8: Invasive mechanical ventilation plus other organ support	6 (4.2%)	145 (13.7%)
9: Death	9 (6.3%)	91 (8.6%)

Abbreviations: HFNC = high-flow nasal cannula; IMV = invasive mechanical ventilation; NIV = non-invasive ventilation; O2 = oxygen

[a] Adjusted for age group (18-49, 50-64, ≥65 years), sex, race and ethnicity, number of underlying conditions by category (0, 1, 2, 3, ≥4).