

Clinical outcomes associated with Omicron (B.1.1.529) variant and BA.1/BA.1.1 or BA.2 subvariant infection in southern California

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Table S1: Concordance of SGTF infection status with Omicron or Delta variant detection.

Period	S gene detection	Variant detection		Predictive accuracy of SGTF proxy definition for lineage (Omicron/Delta and BA.2/BA.1*)
December, 2021–January, 2022		<u>Delta (B.1.617.2)</u>	<u>Omicron (B.1.1.529)</u>	
	Detected (non-SGTF)	1092	3	99.7%
February–March, 2022	Not detected (SGTF)	0	382	100%
		<u>BA.2</u>	<u>BA.1* (BA.1/BA.1.1/B.1.1.529)</u>	
	Detected (non-SGTF)	203	7	96.7%
	Not detected (SGTF)	0	1,140	100%

SGTF: S gene target failure.

Table S2: Demographic and clinical characteristics of cases tested in outpatient settings with and without SGTF, 15 December, 2021 to 17 January, 2022.

Characteristic	Number of cases (%)		Odds ratio (95% CI), Omicron vs. Delta	
	No SGTF (Delta) N=23,305	SGTF (Omicron) N=222,688	Unadjusted	Adjusted ¹
Age ¹				
<1 year	391 (1.7)	1,174 (0.5)	0.23 (0.21, 0.26)	0.37 (0.33, 0.42)
1-4 year	1,023 (4.4)	6,579 (3.0)	0.51 (0.47, 0.54)	0.74 (0.68, 0.81)
5-9 years	1,321 (5.7)	12,235 (5.5)	0.74 (0.69, 0.79)	0.95 (0.88, 1.03)
10-19 years	3,218 (13.8)	28,510 (12.8)	0.72 (0.69, 0.76)	0.76 (0.72, 0.80)
20-29 years	3,096 (13.3)	37,894 (17.0)	1.10 (1.05, 1.16)	1.11 (1.05, 1.16)
30-39 years	3,942 (16.9)	45,165 (20.3)	ref.	ref.
40-49 years	3,770 (16.2)	37,685 (16.9)	0.84 (0.80, 0.88)	0.80 (0.76, 0.84)
50-59 years	3,310 (14.2)	29,205 (13.1)	0.72 (0.68, 0.75)	0.67 (0.63, 0.70)
60-69 years	1,973 (8.5)	15,767 (7.1)	0.63 (0.60, 0.67)	0.56 (0.53, 0.60)
70-79 years	802 (3.4)	5,946 (2.7)	0.58 (0.53, 0.63)	0.50 (0.45, 0.54)
≥80 years	264 (1.1)	1,564 (0.7)	0.45 (0.39, 0.52)	0.41 (0.35, 0.47)
Sex				
Female	12,926 (55.5)	123,227 (55.3)	ref.	ref.
Male	10,379 (44.5)	99,461 (44.7)	1.01 (0.98, 1.03)	1.03 (1.00, 1.06)
Race/ethnicity				
White, non-Hispanic	5,788 (24.8)	49,411 (22.2)	ref.	ref.
Black, non-Hispanic	1,552 (6.7)	17,066 (7.7)	1.28 (1.21, 1.36)	1.36 (1.28, 1.45)
Hispanic	11,792 (50.6)	111,574 (50.1)	1.03 (0.99, 1.06)	1.00 (0.96, 1.03)
Asian/Pacific Islander	1,954 (8.4)	23,406 (10.5)	1.33 (1.26, 1.40)	1.12 (1.06, 1.18)
Other, mixed race, or unknown race	2,219 (9.5)	21,231 (9.5)	1.09 (1.03, 1.15)	0.99 (0.93, 1.04)
Community median income ²				
<\$50,000	3,427 (15.0)	34,364 (15.7)	1.03 (0.99, 1.07)	1.03 (0.99, 1.08)
\$50,000-\$99,999	14,271 (62.4)	133,710 (60.9)	ref.	ref.
\$100,000-\$149,999	4,613 (20.2)	45,318 (20.6)	1.09 (1.05, 1.13)	1.07 (1.03, 1.11)
≥\$150,000	551 (2.4)	6,131 (2.8)	1.24 (1.13, 1.35)	1.19 (1.09, 1.30)
Cigarette smoking ²				
Never smoker	14,172 (81.3)	134,059 (81.7)	ref.	ref.
Current smoker	723 (4.1)	6,865 (4.2)	1.02 (0.94, 1.09)	0.99 (0.91, 1.06)
Former smoker	2,535 (14.5)	23,150 (14.1)	0.99 (0.95, 1.03)	1.01 (0.97, 1.05)
Body mass index ²				
Underweight (<18.5)	1,808 (10.2)	14,647 (8.8)	0.78 (0.74, 0.82)	0.96 (0.90, 1.02)
Normal weight (18.5-24.9)	4,138 (23.3)	41,117 (24.8)	ref.	ref.
Overweight (25.0-29.9)	4,955 (27.9)	46,796 (28.2)	0.94 (0.90, 0.98)	0.95 (0.91, 0.99)
Obese (≥30)	6,863 (38.6)	63,212 (38.1)	0.89 (0.85, 0.92)	0.92 (0.88, 0.95)
Prior year outpatient visits				
0-4	7,973 (34.2)	80,388 (36.1)	ref.	ref.
5-9	6,190 (26.6)	61,656 (27.7)	1.00 (0.97, 1.04)	0.97 (0.93, 1.00)
10-14	3,504 (15.0)	31,883 (14.3)	0.91 (0.88, 0.95)	0.90 (0.86, 0.94)
15-19	1,948 (8.4)	17,634 (7.9)	0.91 (0.86, 0.96)	0.91 (0.86, 0.96)
≥20-29	3,690 (15.8)	31,127 (14.0)	0.84 (0.80, 0.87)	0.87 (0.83, 0.92)
Prior year ED visits				
0	18,402 (79.0)	184,658 (82.9)	ref.	ref.
1	3,340 (14.3)	27,489 (12.3)	0.82 (0.78, 0.85)	0.88 (0.85, 0.92)
2	957 (4.1)	6,632 (3.0)	0.68 (0.63, 0.73)	0.76 (0.71, 0.82)
≥3	606 (2.6)	3,909 (1.8)	0.62 (0.57, 0.68)	0.73 (0.67, 0.81)
Prior year inpatient admissions				
0	22,497 (96.5)	216,532 (97.2)	ref.	ref.
1	431 (1.8)	3,330 (1.5)	0.78 (0.70, 0.86)	0.88 (0.79, 0.98)
2	209 (0.9)	1,388 (0.6)	0.67 (0.58, 0.77)	0.78 (0.67, 0.90)
≥3	168 (0.7)	1,438 (0.6)	0.84 (0.71, 0.99)	1.00 (0.85, 1.19)
Charlson comorbidity index				
0	18,502 (79.4)	181,317 (81.4)	ref.	ref.
1-2	3,836 (16.5)	34,691 (15.6)	0.89 (0.86, 0.93)	0.98 (0.94, 1.02)
3-5	710 (3.0)	5,051 (2.3)	0.67 (0.62, 0.73)	0.87 (0.79, 0.95)
≥6	257 (1.1)	1,629 (0.7)	0.59 (0.52, 0.68)	0.82 (0.70, 0.95)
Prior SARS-CoV-2 infection ³				
No documented previous infection	23,221 (99.6)	221,525 (99.5)	ref.	ref.
Documented previous infection	84 (0.4)	1,163 (0.5)	1.55 (1.23, 1.94)	1.75 (1.39, 2.19)
COVID-19 vaccination				
Unvaccinated	9,802 (42.1)	65,480 (29.4)	ref.	ref.
Ad.26.COVS.S—1 dose	717 (3.1)	6,874 (3.1)	1.50 (1.39, 1.63)	1.56 (1.44, 1.70)
Ad.26.COVS.S—with any booster dose	170 (0.7)	2,329 (1.0)	2.04 (1.74, 2.40)	2.32 (1.97, 2.72)
BNT162b2 or mRNA-1273—1 dose	646 (2.8)	6,266 (2.8)	1.43 (1.31, 1.56)	1.38 (1.27, 1.51)

BNT162b2 or mRNA-1273—2 doses (≥ 180 days prior)	7,492 (32.1)	81,266 (36.5)	1.68 (1.63, 1.74)	1.75 (1.69, 1.82)
BNT162b2 or mRNA-1273—2 doses (91-180 days prior)	1,600 (6.9)	18,409 (8.3)	1.68 (1.58, 1.77)	1.67 (1.58, 1.77)
BNT162b2 or mRNA-1273—2 doses (≤ 90 days prior)	622 (2.7)	8,548 (3.8)	2.04 (1.87, 2.22)	1.95 (1.79, 2.13)
BNT162b2 or mRNA-1273—3 doses	2,256 (9.7)	33,516 (15.1)	2.11 (2.01, 2.21)	2.60 (2.47, 2.75)

SGTF: S gene target failure, here interpreted as a proxy for SARS-CoV-2 variant; CI: Confidence interval.

¹Logistic regression models control for all variables listed in the table, and define intercepts for testing date for both unadjusted and adjusted analyses.

²Multiple imputation was used to address missing data; numbers may not add to column totals where missing values occur. The number of missing observations for each variable is specified in **Table S21**.

³Previous infection defined by any positive test result or diagnosis ≥ 90 days prior to the date of the current test.

Table S3: Comorbid conditions among cases tested in outpatient settings with and without SGTF, 15 December, 2021 to 17 January, 2022.

Condition	Outpatient tested cases, <i>n</i> (%)				Symptomatic hospitalized cases, <i>n</i> (%)			
	No SGTF (Delta)	SGTF (Omicron)	Odds ratio (95% CI), Omicron vs. Delta		No SGTF (Delta)	SGTF (Omicron)	Odds ratio (95% CI), Omicron vs. Delta	
			Unadjusted	Adjusted ¹			Unadjusted	Adjusted ¹
	<i>N</i> =23,305	<i>N</i> =222,688			<i>N</i> =323	<i>N</i> =1,239		
Myocardial infarction	167 (0.7)	1,054 (0.5)	0.60 (0.51, 0.70)	0.87 (0.73, 1.05)	18 (5.6)	33 (2.7)	0.44 (0.23, 0.84)	0.69 (0.31, 1.53)
Congestive heart failure	244 (1.0)	1,499 (0.7)	0.59 (0.52, 0.68)	0.94 (0.80, 1.10)	24 (7.4)	74 (6.0)	0.81 (0.48, 1.36)	1.17 (0.60, 2.30)
Peripheral vascular disease	826 (3.5)	5,742 (2.6)	0.67 (0.62, 0.72)	0.97 (0.88, 1.07)	55 (17.0)	156 (12.6)	0.65 (0.45, 0.94)	1.05 (0.61, 1.80)
Cerebrovascular disease	178 (0.8)	1,273 (0.6)	0.70 (0.59, 0.82)	1.06 (0.89, 1.26)	14 (4.3)	31 (2.5)	0.63 (0.31, 1.29)	1.02 (0.45, 2.35)
Diabetes—controlled	1,303 (5.6)	12,004 (5.4)	0.90 (0.85, 0.96)	0.99 (0.92, 1.05)	32 (9.9)	146 (11.8)	1.20 (0.77, 1.86)	1.16 (0.74, 1.83)
Diabetes—uncontrolled	739 (3.2)	5,432 (2.4)	0.71 (0.65, 0.76)	0.92 (0.83, 1.01)	41 (12.7)	139 (11.2)	0.85 (0.56, 1.27)	0.88 (0.52, 1.47)
Liver disease—mild	566 (2.4)	4,848 (2.2)	0.86 (0.79, 0.94)	0.98 (0.90, 1.08)	11 (3.4)	67 (5.4)	1.71 (0.85, 3.44)	1.66 (0.84, 3.26)
Liver disease—moderate to severe	32 (0.1)	148 (0.1)	0.46 (0.31, 0.68)	0.72 (0.48, 1.07)	1 (0.3)	9 (0.7)	1.55 (0.19, 12.8)	1.85 (0.20, 17.1)
Renal disease	515 (2.2)	3,539 (1.6)	0.67 (0.61, 0.73)	0.93 (0.83, 1.05)	33 (10.2)	128 (10.3)	1.06 (0.68, 1.65)	1.41 (0.77, 2.60)
Chronic obstructive pulmonary disease	1,864 (8.0)	16,071 (7.2)	0.88 (0.84, 0.93)	0.98 (0.87, 1.10)	58 (18.0)	162 (13.1)	0.62 (0.43, 0.88)	0.43 (0.22, 0.86)
Asthma	1,741 (7.5)	15,219 (6.8)	0.90 (0.85, 0.95)	0.99 (0.88, 1.11)	41 (12.7)	135 (10.9)	0.78 (0.52, 1.16)	1.58 (0.75, 3.31)
Apnea	801 (3.4)	6,743 (3.0)	0.86 (0.80, 0.92)	0.99 (0.92, 1.08)	25 (7.7)	96 (7.7)	0.96 (0.59, 1.58)	1.26 (0.73, 2.16)
Hyperlipidemia	3,522 (15.1)	30,348 (13.6)	0.85 (0.82, 0.89)	1.02 (0.97, 1.07)	109 (33.7)	342 (27.6)	0.68 (0.51, 0.91)	0.85 (0.59, 1.22)
Hypothyroid	741 (3.2)	5,904 (2.7)	0.81 (0.75, 0.88)	0.95 (0.88, 1.04)	19 (5.9)	84 (6.8)	1.09 (0.62, 1.89)	1.07 (0.61, 1.88)
Depression	1,868 (8.0)	17,715 (8.0)	1.01 (0.96, 1.06)	1.03 (0.97, 1.09)	37 (11.5)	155 (12.5)	1.25 (0.82, 1.89)	1.21 (0.77, 1.89)
Dementia	52 (0.2)	313 (0.1)	0.55 (0.41, 0.74)	0.93 (0.68, 1.27)	4 (1.2)	14 (1.1)	0.80 (0.24, 2.67)	1.03 (0.26, 4.10)
Rheumatic disease	203 (0.9)	1,568 (0.7)	0.78 (0.68, 0.91)	0.90 (0.77, 1.05)	3 (0.9)	33 (2.7)	4.01 (1.04, 15.5)	2.67 (0.84, 8.53)
Peptic ulcer disease	43 (0.2)	216 (0.1)	0.51 (0.36, 0.71)	0.69 (0.49, 0.97)	3 (0.9)	11 (0.9)	1.17 (0.29, 4.74)	0.91 (0.18, 4.70)
Paraplegia and hemiplegia	37 (0.2)	272 (0.1)	0.72 (0.51, 1.03)	0.98 (0.68, 1.41)	3 (0.9)	8 (0.6)	0.70 (0.16, 3.14)	0.43 (0.10, 1.85)
Organ transplantation	44 (0.2)	252 (0.1)	0.55 (0.40, 0.77)	0.61 (0.43, 0.87)	2 (0.6)	28 (2.3)	2.71 (0.63, 11.7)	0.72 (0.18, 2.85)
HIV	13 (0.1)	133 (0.1)	0.99 (0.56, 1.75)	0.96 (0.54, 1.72)	0 (0.0)	1 (0.1)	—	—
Cancer—Metastatic carcinoma	74 (0.3)	592 (0.3)	0.81 (0.63, 1.04)	1.05 (0.81, 1.35)	4 (1.2)	14 (1.1)	0.82 (0.25, 2.70)	1.18 (0.35, 3.93)
Cancer—other	289 (1.2)	2,234 (1.0)	0.77 (0.68, 0.88)	0.96 (0.84, 1.09)	13 (4.0)	59 (4.8)	1.09 (0.57, 2.07)	1.17 (0.61, 2.23)
Other immunocompromising or immune suppressing condition	541 (2.3)	4,778 (2.1)	0.91 (0.84, 1.00)	1.04 (0.95, 1.15)	17 (5.3)	91 (7.3)	1.55 (0.87, 2.75)	1.45 (0.77, 2.72)

SGTF: S gene target failure, here interpreted as a proxy for SARS-CoV-2 variant; CI: Confidence interval.

¹Logistic regression models control for all variables listed in **Table S2**, and define intercepts for testing date for both unadjusted and adjusted analyses.

Table S4: Combined history of documented SARS-CoV-2 infection and COVID-19 vaccination among cases diagnosed in outpatient settings with and without SGTF, 15 December, 2021 to 17 January, 2022.

Vaccination history	History of prior infection	Number of cases (%)		Odds ratio (95% CI), Omicron vs. Delta	
		No SGTF (Delta) N=23,305	SGTF (Omicron) N=222,688	Unadjusted	Adjusted ¹
Unvaccinated	No documented previous infection	9,760 (41.9)	64,920 (29.2)	ref.	ref.
	Documented previous infection	42 (0.2)	560 (0.3)	2.13 (1.54, 2.94)	2.14 (1.55, 2.95)
Ad.26.COVS.S—1 dose	No documented previous infection	716 (3.1)	6,825 (3.1)	1.50 (1.38, 1.63)	1.56 (1.43, 1.69)
	Documented previous infection ³	1 (<0.1)	49 (<0.1)	9.10 (1.25, 66.5)	8.58 (1.19, 61.9)
Ad.26.COVS.S—with any booster dose	No documented previous infection	169 (0.7)	2,324 (1.0)	2.06 (1.76, 2.42)	2.33 (1.98, 2.74)
	Documented previous infection	1 (<0.1)	5 (<0.1)	0.65 (0.08, 5.57)	0.77 (0.09, 6.62)
BNT162b2 or mRNA-1973—1 dose	No documented previous infection	644 (2.8)	6,230 (2.8)	1.43 (1.32, 1.56)	1.38 (1.27, 1.51)
	Documented previous infection	2 (<0.1)	36 (<0.1)	3.10 (0.73, 13.1)	3.11 (0.74, 13.2)
BNT162b2 or mRNA-1973—2 doses (>180 days prior)	No documented previous infection	7,477 (32.1)	81,039 (36.4)	1.69 (1.64, 1.75)	1.76 (1.69, 1.82)
	Documented previous infection			2.28 (1.34, 3.87)	2.43 (1.43, 4.12)
BNT162b2 or mRNA-1973—2 doses (91-180 days prior)	No documented previous infection	1,589 (6.8)	18,255 (8.2)	1.68 (1.59, 1.78)	1.68 (1.58, 1.78)
	Documented previous infection	11 (<0.1)	154 (0.1)	2.03 (1.10, 3.78)	2.10 (1.13, 3.91)
BNT162b2 or mRNA-1973—2 doses (≤90 days prior)	No documented previous infection	619 (2.7)	8,466 (3.8)	2.03 (1.87, 2.22)	1.94 (1.78, 2.12)
	Documented previous infection	3 (<0.1)	82 (<0.1)	6.06 (1.84, 19.9)	6.26 (1.86, 21.0)
BNT162b2 or mRNA-1973—3 doses	No documented previous infection	2,247 (9.6)	33,466 (15.0)	2.12 (2.02, 2.23)	2.62 (2.48, 2.76)
	Documented previous infection	9 (<0.1)	50 (<0.1)	0.91 (0.43, 1.93)	1.16 (0.55, 2.45)

SGTF: S gene target failure, here interpreted as a proxy for SARS-CoV-2 variant; CI: confidence interval.

¹Logistic regression models control for all variables listed in **Table S2**, and define intercepts for testing date for both unadjusted and adjusted analyses.

Table S5: Demographic and clinical characteristics of cases tested in outpatient settings with and without SGTF, 3 February to 17 March, 2022.

Characteristic	Number of cases (%)		Odds ratio (95% CI), BA.2 vs. BA.1*	
	No SGTF (BA.2) N=1,905	SGTF (BA.1*) N=12,756	Unadjusted	Adjusted ¹
Age ¹				
<1 year	53 (2.8)	157 (1.2)	2.95 (2.09, 4.17)	2.75 (1.90, 3.99)
1-4 year	104 (5.5)	608 (4.8)	1.46 (1.14, 1.88)	1.47 (1.04, 2.08)
5-9 years	89 (4.7)	904 (7.1)	0.82 (0.63, 1.06)	1.03 (0.74, 1.43)
10-19 years	217 (11.4)	1,432 (11.2)	1.29 (1.06, 1.56)	1.44 (1.17, 1.78)
20-29 years	197 (10.3)	1,393 (10.9)	1.11 (0.91, 1.36)	1.12 (0.91, 1.37)
30-39 years	315 (16.5)	2,421 (19.0)	ref.	ref.
40-49 years	271 (14.2)	2,090 (16.4)	1.03 (0.86, 1.23)	1.02 (0.85, 1.22)
50-59 years	272 (14.3)	1,624 (12.7)	1.36 (1.14, 1.64)	1.36 (1.13, 1.63)
60-69 years	230 (12.1)	1,240 (9.7)	1.54 (1.27, 1.87)	1.51 (1.23, 1.85)
70-79 years	102 (5.4)	632 (5.0)	1.25 (0.97, 1.61)	1.21 (0.91, 1.59)
≥80 years	39 (2.0)	218 (1.7)	1.45 (0.99, 2.12)	1.32 (0.87, 2.00)
Sex				
Female	1,040 (54.6)	6,844 (53.7)	ref.	ref.
Male	865 (45.4)	5,912 (46.3)	0.99 (0.89, 1.09)	0.98 (0.88, 1.08)
Race/ethnicity				
White, non-Hispanic	504 (26.5)	3,354 (26.3)	ref.	ref.
Black, non-Hispanic	109 (5.7)	737 (5.8)	1.00 (0.79, 1.26)	1.01 (0.80, 1.28)
Hispanic	858 (45.0)	6,041 (47.4)	0.97 (0.86, 1.10)	1.01 (0.89, 1.16)
Asian/Pacific Islander	256 (13.4)	1,489 (11.7)	1.06 (0.89, 1.26)	1.15 (0.96, 1.37)
Other, mixed race, or unknown race	178 (9.3)	1,135 (8.9)	1.06 (0.88, 1.29)	1.15 (0.95, 1.41)
Community median income ²				
<\$50,000	306 (16.5)	1,950 (15.6)	1.11 (0.96, 1.27)	1.11 (0.97, 1.29)
\$50,000-\$99,999	1,059 (57.1)	7,459 (59.7)	ref.	ref.
\$100,000-\$149,999	445 (24.0)	2,694 (21.6)	1.08 (0.95, 1.22)	1.07 (0.94, 1.22)
≥\$150,000	46 (2.5)	390 (3.1)	0.84 (0.59, 1.19)	0.79 (0.56, 1.13)
Cigarette smoking ²				
Never smoker	1,120 (79.0)	7,796 (80.8)	ref.	ref.
Current smoker	63 (4.4)	340 (3.5)	1.19 (0.93, 1.51)	1.23 (0.95, 1.57)
Former smoker	234 (16.5)	1,512 (15.7)	1.10 (0.95, 1.27)	1.11 (0.95, 1.30)
Body mass index ²				
Underweight (<18.5)	156 (10.4)	1,226 (12.0)	0.92 (0.75, 1.12)	0.93 (0.71, 1.22)
Normal weight (18.5-24.9)	374 (24.9)	2,436 (23.8)	ref.	ref.
Overweight (25.0-29.9)	441 (29.4)	2,895 (28.3)	1.03 (0.88, 1.20)	1.01 (0.85, 1.18)
Obese (≥30)	530 (35.3)	3,669 (35.9)	1.00 (0.87, 1.15)	0.98 (0.84, 1.14)
Prior year outpatient visits				
0-4	480 (25.2)	3,518 (27.6)	ref.	ref.
5-9	465 (24.4)	3,343 (26.2)	1.00 (0.87, 1.16)	0.98 (0.85, 1.14)
10-14	333 (17.5)	1,990 (15.6)	1.23 (1.05, 1.43)	1.15 (0.97, 1.36)
15-19	183 (9.6)	1,270 (10.0)	1.07 (0.88, 1.29)	0.97 (0.79, 1.19)
≥20	444 (23.3)	2,635 (20.7)	1.22 (1.05, 1.41)	1.09 (0.92, 1.31)
Prior year ED visits				
0	1,434 (75.3)	10,264 (80.5)	ref.	ref.
1	302 (15.9)	1,704 (13.4)	1.29 (1.12, 1.48)	1.25 (1.08, 1.45)
2	98 (5.1)	467 (3.7)	1.56 (1.23, 1.97)	1.51 (1.18, 1.92)
≥3	71 (3.7)	321 (2.5)	1.66 (1.26, 2.19)	1.64 (1.22, 2.20)
Prior year inpatient admissions				
0	1,829 (96.0)	12,265 (96.2)	ref.	ref.
1	34 (1.8)	254 (2.0)	0.89 (0.61, 1.29)	0.74 (0.51, 1.09)
2	19 (1.0)	115 (0.9)	1.13 (0.68, 1.86)	0.99 (0.59, 1.65)
≥3	23 (1.2)	122 (1.0)	1.20 (0.75, 1.92)	1.00 (0.62, 1.63)
Charlson comorbidity index				
0	1,455 (76.4)	9,884 (77.5)	ref.	ref.
1-2	336 (17.6)	2,231 (17.5)	1.05 (0.92, 1.20)	0.93 (0.81, 1.08)
3-5	74 (3.9)	466 (3.7)	1.06 (0.81, 1.38)	0.80 (0.59, 1.09)
≥6	40 (2.1)	175 (1.4)	1.53 (1.06, 2.21)	1.11 (0.73, 1.68)
Prior SARS-CoV-2 infection ³				
No documented previous infection	1,898 (99.6)	12,681 (99.4)	ref.	ref.
Documented previous infection	7 (0.4)	75 (0.6)	0.68 (0.30, 1.52)	0.70 (0.31, 1.60)
COVID-19 vaccination				
Unvaccinated	594 (31.2)	3,858 (30.2)	ref.	ref.
Ad.26.COV2.S—1 dose	34 (1.8)	273 (2.1)	0.78 (0.53, 1.14)	0.84 (0.57, 1.25)
Ad.26.COV2.S—with any booster dose	38 (2.0)	203 (1.6)	1.11 (0.77, 1.62)	1.14 (0.78, 1.67)
BNT162b2 or mRNA-1273—1 dose	33 (1.7)	287 (2.2)	0.73 (0.49, 1.07)	0.79 (0.54, 1.17)
BNT162b2 or mRNA-1273—2 doses (≥180 days prior)	424 (22.3)	2,826 (22.2)	0.93 (0.81, 1.07)	0.99 (0.85, 1.16)
BNT162b2 or mRNA-1273—2 doses (91-180 days prior)	94 (4.9)	863 (6.8)	0.72 (0.57, 0.91)	0.77 (0.60, 0.99)
BNT162b2 or mRNA-1273—2 doses (≤90 days prior)	47 (2.5)	625 (4.9)	0.48 (0.35, 0.65)	0.53 (0.38, 0.74)
BNT162b2 or mRNA-1273—3 doses	641 (33.6)	3,821 (30.0)	0.95 (0.83, 1.07)	0.97 (0.83, 1.13)

SGTF: S gene target failure, here interpreted as a proxy for SARS-CoV-2 variant.

¹Logistic regression models control for all variables listed in the table, and define intercepts for testing date for both unadjusted and adjusted analyses.

²Multiple imputation was used to address missing data; numbers may not add to column totals where missing values occur. The number of missing observations for each variable is specified in **Table S21**.

³Previous infection defined by any positive test result or diagnosis ≥ 90 days prior to the date of the current test.

Table S6: Combined history of documented SARS-CoV-2 infection and COVID-19 vaccination among cases diagnosed in outpatient settings with and without SGTF, 3 February to 17 March, 2022.

Vaccination history	History of prior infection	Number of cases (%)		Odds ratio (95% CI), BA.2 vs. BA.1*	
		No SGTF (BA.2) N=1,905	SGTF (BA.1*) N=12,756	Unadjusted	Adjusted ¹
Unvaccinated	No documented previous infection	589 (30.9)	3,821 (30.0)	ref.	ref.
	Documented previous infection	5 (0.3)	37 (0.3)	0.91 (0.33, 2.45)	1.05 (0.38, 2.90)
Ad.26.COV2.S—1 dose	No documented previous infection	34 (1.8)	272 (2.1)	0.78 (0.53, 1.15)	0.85 (0.57, 1.25)
	Documented previous infection ³	0 (0.0)	1 (<0.1)	--	--
Ad.26.COV2.S—with any booster dose	No documented previous infection	38 (2.0)	202 (1.6)	1.12 (0.77, 1.62)	1.15 (0.78, 1.69)
	Documented previous infection	0 (0.0)	1 (<0.1)	--	--
BNT162b2 or mRNA-1973—1 dose	No documented previous infection	33 (1.7)	285 (2.2)	0.73 (0.49, 1.08)	0.80 (0.54, 1.18)
	Documented previous infection	0 (0.0)	2 (<0.1)	--	--
BNT162b2 or mRNA-1973—2 doses (>180 days prior)	No documented previous infection	423 (22.2)	2,810 (22.0)	0.93 (0.81, 1.07)	1.00 (0.85, 1.17)
	Documented previous infection	1 (0.1)	16 (0.1)	0.45 (0.06, 3.48)	0.43 (0.06, 3.33)
BNT162b2 or mRNA-1973—2 doses (91-180 days prior)	No documented previous infection	93 (4.9)	853 (6.7)	0.72 (0.57, 0.91)	0.77 (0.60, 0.99)
	Documented previous infection	1 (0.1)	10 (0.1)	0.66 (0.08, 5.20)	0.68 (0.08, 5.50)
BNT162b2 or mRNA-1973—2 doses (≤90 days prior)	No documented previous infection	47 (2.5)	624 (4.9)	0.48 (0.35, 0.66)	0.53 (0.38, 0.74)
	Documented previous infection	0 (0.0)	1 (<0.1)	--	--
BNT162b2 or mRNA-1973—3 doses	No documented previous infection	641 (33.6)	3,814 (29.9)	0.95 (0.83, 1.07)	0.97 (0.83, 1.14)
	Documented previous infection	0 (0.0)	7 (0.1)	--	--

SGTF: S gene target failure, here interpreted as a proxy for SARS-CoV-2 variant; CI: confidence interval.

¹Logistic regression models control for all variables listed in **Table S2**, and define intercepts for testing date for both unadjusted and adjusted analyses.

Table S7: Occurrence of severe clinical outcomes among cases with and without SGTF, 15 December, 2021 to 17 January, 2022.

Outcome	Case population ¹	Cumulative events over observed follow-up (n of events per 1000 cases)		Event rate per 10,000 person-days observed (n of events/person-days at risk)		Hazard ratio (95% CI), Omicron vs. Delta	
		No SGTF (Delta)	SGTF (Omicron)	No SGTF (Delta)	SGTF (Omicron)	Unadjusted	Adjusted
Any hospital admission	Cases tested in outpatient settings	241 (10.3)	991 (4.5)	3.61 (241/667,630)	1.55 (991/6,413,416)	0.48 (0.42, 0.56)	0.59 (0.51, 0.69)
	All cases	369 (15.7)	1,642 (7.3)	5.53 (369/667,696)	2.56 (1,642/6,413,759)	0.50 (0.44, 0.56)	0.61 (0.54, 0.68)
Symptomatic hospital admission ¹	Cases tested in outpatient settings	226 (9.7)	878 (3.9)	3.39 (226/667,630)	1.37 (878/6,413,416)	0.46 (0.40, 0.54)	0.59 (0.51, 0.68)
	All cases	323 (13.7)	1,239 (5.5)	4.84 (323/667,696)	1.93 (1,239/6,413,759)	0.44 (0.38, 0.50)	0.55 (0.49, 0.62)
ICU admission	Cases tested in outpatient settings	26 (1.1)	51 (0.2)	0.19 (26/1,363,726)	0.04 (51/13,062,884)	0.27 (0.15, 0.40)	0.50 (0.29, 0.87)
	All cases	29 (1.2)	57 (0.3)	0.21 (29/1,371,050)	0.04 (57/13,100,749)	0.24 (0.15, 0.39)	0.48 (0.29, 0.81)
Mechanical ventilation	Cases tested in outpatient settings	17 (0.7)	24 (0.1)	0.12 (17/1,364,195)	0.02 (24/13,064,223)	0.18 (0.09, 0.35)	0.36 (0.18, 0.72)
	All cases	19 (0.8)	26 (0.1)	0.14 (19/1,371,577)	0.02 (26/13,102,322)	0.17 (0.09, 0.33)	0.32 (0.17, 0.62)
Death	Cases tested in outpatient settings	19 (0.8)	19 (0.1)	0.14 (19/1,364,392)	0.01 (19/13,064,699)	0.12 (0.06, 0.23)	0.21 (0.10, 0.44)
	All cases	19 (0.8)	19 (0.1)	0.14 (19/1,371,886)	0.01 (19/13,102,914)	0.12 (0.06, 0.23)	0.21 (0.10, 0.44)

SGTF: S gene target failure, here interpreted as a proxy for SARS-CoV-2 variant; CI: confidence interval. Sample includes 23,305 and 222,688 cases with Delta and Omicron variant infection, respectively, diagnosed in outpatient settings.

¹We define symptomatic hospital admissions as those occurring among cases with respiratory symptom onset dates on or ≤14 days before the date of admission.

Table S8: Occurrence of clinical outcomes among cases with and without SGTF, without symptoms at the time of their first positive test, 15 December, 2021 to 17 January, 2022.

Outcome	Case population ¹	Cumulative events over observed follow-up (<i>n</i> of events per 1,000 cases)		Event rate per 10,000 person-days observed (<i>n</i> of events/person-days at risk)		Hazard ratio (95% CI), Omicron vs. Delta	
		No SGTF (Delta)	SGTF (Omicron)	No SGTF (Delta)	SGTF (Omicron)	Unadjusted	Adjusted
Onset of respiratory symptoms	Cases tested in outpatient settings without symptoms	574 (13.3)	5,720 (11.6)	0.20 (574/280,118)	0.18 (5,720/3,109,842)	0.95 (0.87, 1.04)	0.88 (0.81, 0.96)
	All cases without symptoms at point of testing	581 (13.4)	5,787 (11.7)	0.21 (581/281,047)	0.19 (5,787/3,119,788)	0.95 (0.87, 1.04)	0.89 (0.81, 0.97)
Any hospital admission	Cases tested in outpatient settings without symptoms	28 (6.5)	179 (3.6)	2.27 (28/123,523)	1.26 (179/1,416,427)	0.57 (0.38, 0.86)	0.69 (0.46, 1.05)
	All cases without symptoms at point of testing	45 (10.4)	356 (7.2)	3.64 (45/123,532)	2.51 (356/1,416,516)	0.71 (0.52, 0.98)	0.83 (0.60, 1.15)
Symptomatic hospital admission ¹	Cases tested in outpatient settings without symptoms	13 (3.0)	66 (1.3)	1.05 (13/123,523)	0.47 (66/1,416,427)	0.53 (0.35, 0.80)	0.65 (0.43, 0.98)
	All cases without symptoms at point of testing	13 (3.0)	66 (1.3)	1.05 (13/123,532)	0.47 (66/1,416,516)	0.53 (0.35, 0.80)	0.65 (0.43, 0.98)
ICU admission	Cases tested in outpatient settings without symptoms	1 (0.2)	8 (0.2)	0.04 (1/251,816)	0.03 (8/2,885,008)	0.59 (0.07, 4.70)	--
	All cases without symptoms at point of testing	1 (0.2)	8 (0.2)	0.04 (1/252,819)	0.03 (8/2,895,452)	0.59 (0.07, 4.71)	--
Mechanical ventilation	Cases tested in outpatient settings without symptoms	0 (0.0)	4 (0.1)	0.00 (0/251,978)	0.01 (4/2,885,243)	--	--
	All cases without symptoms at point of testing	0 (0.0)	4 (0.1)	0.00 (0/252,981)	0.01 (4/2,895,686)	--	--
Death	Cases tested in outpatient settings without symptoms	0 (0.0)	0 (0.0)	0.00 (0/251,978)	0.00 (0/2,885,381)	--	--
	All cases without symptoms at point of testing	0 (0.0)	0 (0.0)	0.00 (0/252,981)	0.00 (0/2,895,824)	--	--

SGTF: S gene target failure, here interpreted as a proxy for SARS-CoV-2 variant; CI: confidence interval.

Symptoms data were collected from free-text fields of patient EHRs, including data from clinical notes and from responses to questionnaires addressing symptoms in the 14 days before testing which all patients must complete to receive a test. Note that because lengths of follow-up differ between SGTF and non-SGTF cases, clinical risk periods over which cumulative events and event rates are summarized may differ between the two case populations.

¹We define symptomatic hospital admissions as those occurring among cases with respiratory symptom onset dates on or ≤14 days before the date of admission.

Table S9: Comparison of associations of SGTF with clinical outcomes across differing missing-data analysis strategies, 15 December, 2021 to 17 January, 2022.

Outcome	Case population ¹	Primary analysis: Adjusted hazard ratio (95% CI), Omicron vs. Delta	Complete case analysis: Adjusted hazard ratio (95% CI), Omicron vs. Delta	Participants enrolled ≥1 year: Adjusted hazard ratio (95% CI), Omicron vs. Delta
Any hospital admission	Cases tested in outpatient settings	0.59 (0.51, 0.69)	0.65 (0.55, 0.76)	0.59 (0.51, 0.70)
	All cases	0.61 (0.54, 0.68)	0.66 (0.58, 0.75)	0.62 (0.55, 0.70)
Symptomatic hospital admission ¹	Cases tested in outpatient settings	0.59 (0.51, 0.68)	0.64 (0.54, 0.75)	0.59 (0.50, 0.69)
	All cases	0.55 (0.49, 0.62)	0.61 (0.53, 0.70)	0.56 (0.49, 0.64)
ICU admission	Cases tested in outpatient settings	0.50 (0.29, 0.87)	0.53 (0.30, 0.95)	0.51 (0.29, 0.91)
	All cases	0.48 (0.29, 0.81)	0.50 (0.29, 0.87)	0.52 (0.29, 0.92)
Mechanical ventilation	Cases tested in outpatient settings	0.36 (0.18, 0.72)	0.32 (0.16, 0.65)	0.32 (0.16, 0.65)
	All cases	0.32 (0.17, 0.62)	0.30 (0.15, 0.61)	0.34 (0.17, 0.68)
Death	Cases tested in outpatient settings	0.21 (0.10, 0.44)	0.18 (0.08, 0.39)	0.20 (0.09, 0.42)
	All cases	0.21 (0.10, 0.44)	0.18 (0.08, 0.40)	0.20 (0.09, 0.43)

SGTF: S gene target failure, here interpreted as a proxy for SARS-CoV-2 variant; CI: confidence interval. Adjusted Cox proportional hazards models control for all variables listed in **Table S2**, with strata for testing date.

¹We define symptomatic hospital admissions as those occurring among cases with respiratory symptom onset dates on or ≤14 days before the date of admission.

Table S10: Association of SGTF infection status with symptomatic hospitalization within various patient subgroups, 15 December, 2021 to 17 January, 2022.

Characteristic	Cumulative events over observed follow-up, <i>n</i> (total per 1000 cases)		Symptomatic hospitalization rate per 10,000 person-days (<i>n</i> of events/person-days at risk)		Hazard ratio (95% CI), Omicron vs. Delta	
	No SGTF (Delta)	SGTF (Omicron)	No SGTF (Delta)	SGTF (Omicron)	Unadjusted	Adjusted
Age						
0-1 years	3 (4.6)	4 (1.5)	1.6 (3/18,842)	0.5 (4/74,660)	0.44 (0.09, 2.28)	--
2-4 years	0 (0.0)	4 (0.8)	0.0 (0/21,921)	0.3 (4/149,272)	--	--
5-9 years	3 (2.3)	9 (0.7)	0.8 (3/38,152)	0.3 (9/353,778)	0.31 (0.08, 1.19)	--
10-19 years	6 (1.9)	18 (0.6)	0.6 (6/92,954)	0.2 (18/824,353)	0.34 (0.13, 0.89)	0.46 (0.23, 0.91)
20-29 years	15 (4.8)	150 (4.0)	1.7 (15/88,597)	1.4 (150/1,087,778)	0.87 (0.51, 1.48)	1.01 (0.65, 1.55)
30-39 years	31 (7.9)	228 (5.0)	2.7 (31/112,945)	1.8 (228/1,299,085)	0.76 (0.51, 1.12)	0.79 (0.58, 1.06)
40-49 years	38 (10.1)	129 (3.4)	3.5 (38/107,985)	1.2 (128/1,086,231)	0.40 (0.28, 0.59)	0.44 (0.33, 0.60)
50-59 years	44 (13.3)	116 (4.0)	4.7 (44/94,621)	1.4 (116/842,004)	0.36 (0.25, 0.52)	0.49 (0.37, 0.66)
60-69 years	43 (21.8)	107 (6.8)	7.7 (43/56,024)	2.4 (107/453,494)	0.36 (0.25, 0.51)	0.38 (0.29, 0.50)
70-79 years	29 (36.2)	77 (12.9)	12.8 (29/22,600)	4.5 (77/170,397)	0.40 (0.26, 0.63)	0.63 (0.43, 0.19)
≥80 years	12 (45.5)	35 (22.4)	16.3 (12/7,383)	7.9 (35/44,436)	0.60 (0.30, 1.23)	0.77 (0.45, 1.30)
Sex						
Female	119 (9.2)	556 (4.5)	3.2 (119/370,374)	1.6 (556/3,547,248)	0.54 (0.44, 0.67)	0.66 (0.57, 0.77)
Male	107 (10.3)	322 (3.2)	3.6 (107/297,256)	1.1 (322/2,866,168)	0.37 (0.30, 0.47)	0.53 (0.44, 0.64)
Charlson comorbidity index						
0	126 (6.8)	495 (2.7)	2.4 (126/531,196)	0.9 (495/5,225,503)	0.47 (0.38, 0.57)	0.64 (0.54, 0.76)
1-2	59 (15.4)	228 (6.6)	5.4 (59/109,428)	2.3 (228/997,950)	0.51 (0.38, 0.68)	0.58 (0.46, 0.73)
3-5	22 (31.0)	97 (19.2)	11.0 (22/20,036)	6.7 (97/144,063)	0.61 (0.38, 0.99)	0.56 (0.40, 0.79)
≥6	19 (73.9)	58 (35.6)	27.3 (19/6,970)	12.6 (58/45,900)	0.50 (0.29, 0.85)	0.76 (0.49, 1.18)
Previous infection						
No documented previous infection	225 (9.7)	874 (3.9)	3.4 (225/665,208)	1.4 (874/6,379,984)	0.46 (0.40, 0.54)	0.60 (0.54, 0.68)
Documented previous infection	1 (11.9)	4 (3.4)	4.1 (1/2,422)	1.2 (4/33,432)	0.27 (0.03, 2.44)	--
Vaccination						
Unvaccinated	142 (14.5)	272 (4.2)	5.1 (142/279,328)	1.4 (272/1,885,318)	0.36 (0.29, 0.44)	0.47 (0.39, 0.56)
Ad.26.COV2						
Single dose	9 (12.6)	24 (3.5)	4.4 (9/20,471)	1.2 (24/197,871)	0.29 (0.13, 0.64)	0.36 (0.19, 0.70)
With any booster dose	1 (5.9)	10 (4.3)	2.0 (1/4,910)	1.5 (10/67,175)	0.91 (0.11, 7.65)	--
BNT162b2 or mRNA-1273						
Single dose	7 (10.8)	14 (2.2)	3.8 (7/18,476)	0.8 (14/180,371)	0.25 (0.10, 0.63)	0.32 (0.14, 0.76)
2 doses (>180 days prior)	41 (5.5)	308 (3.8)	1.9 (41/215,679)	1.3 (308/2,340,025)	0.44 (0.15, 1.25)	0.65 (0.26, 1.62)
2 doses (91-180 days prior)	8 (5.0)	59 (3.2)	1.7 (8/46,119)	1.1 (59/530,686)	0.72 (0.34, 1.53)	0.71 (0.41, 1.23)
2 doses (≤90 days prior)	5 (22.0)	8 (2.6)	2.8 (5/17,815)	0.9 (22/246,212)	0.72 (0.52, 1.01)	0.85 (0.66, 1.09)
3 doses	13 (5.8)	169 (5.0)	2.0 (13/64,832)	1.7 (169/965,758)	0.91 (0.52, 1.61)	0.78 (0.57, 1.09)

SGTF: S gene target failure, here interpreted as a proxy for SARS-CoV-2 variant; CI: confidence interval. Adjusted Cox proportional hazards models control for all variables listed in **Table S2**, with strata for testing date. We define symptomatic hospital admissions as those occurring among cases with respiratory symptom onset dates on or ≤14 days before the date of admission.

Table S11: Comparison of associations of SGTF with clinical outcomes defined on the basis of the adjusted hazard ratio or adjusted risk ratio, 15 December, 2021 to 17 January, 2022.

Outcome	Case population ¹	Primary analysis: Adjusted hazard ratio (95% CI), Omicron vs. Delta	Log binomial regression analysis: Risk ratio (95% CI), Omicron vs. Delta
Any hospital admission	Cases tested in outpatient settings	0.59 (0.51, 0.69)	0.63 (0.55, 0.72)
	All cases	0.61 (0.54, 0.68)	0.67 (0.60, 0.75)
Symptomatic hospital admission ¹	Cases tested in outpatient settings	0.59 (0.51, 0.68)	0.63 (0.55, 0.72)
	All cases	0.55 (0.49, 0.62)	0.60 (0.54, 0.68)
ICU admission	Cases tested in outpatient settings	0.50 (0.29, 0.87)	0.54 (0.31, 0.94)
	All cases	0.48 (0.29, 0.81)	0.51 (0.30, 0.86)
Mechanical ventilation	Cases tested in outpatient settings	0.36 (0.18, 0.72)	0.35 (0.17, 0.71)
	All cases	0.32 (0.17, 0.62)	0.32 (0.16, 0.62)
Death	Cases tested in outpatient settings	0.21 (0.10, 0.44)	0.20 (0.10, 0.43)
	All cases	0.21 (0.10, 0.44)	0.21 (0.10, 0.43)

SGTF: S gene target failure, here interpreted as a proxy for SARS-CoV-2 variant; CI: confidence interval. Adjusted Cox proportional hazards and log binomial regression models control for all variables listed in **Table S2**, with strata and intercepts for testing date, respectively.

¹We define symptomatic hospital admissions as those occurring among cases with respiratory symptom onset dates on or ≤14 days before the date of admission.

Table S12: Occurrence of severe clinical outcomes among cases tested in outpatient settings with and without SGTF, 3 February to 17 March, 2022.

Outcome	Cumulative events over observed follow-up (<i>n</i> of events per 1000 cases)		Event rate per 10,000 person-days observed (<i>n</i> of events/person-days at risk)		Hazard ratio (95% CI), BA.2 vs. BA.1*	
	No SGTF (BA.2)	SGTF (BA.1*)	No SGTF (BA.2)	SGTF (BA.1*)	Unadjusted	Adjusted
Any hospital admission	28 (14.7)	170 (13.3)	7.01 (28/39,965)	5.16 (170/329,302)	1.38 (0.92, 2.07)	1.26 (0.83, 1.92)
Symptomatic hospital admission ¹	24 (12.6)	147 (11.5)	6.01 (24/39,965)	4.46 (147/329,302)	1.42 (0.92, 2.20)	1.29 (0.82, 2.03)
ICU admission	1 (0.5)	6 (0.5)	0.21 (1/48,374)	0.15 (6/406,887)	1.63 (0.20, 13.8)	--
Mechanical ventilation	1 (0.5)	1 (0.1)	0.21 (1/48,374)	0.02 (1/406,982)	--	--
Death	2 (1.0)	16 (1.3)	0.41 (2/48,367)	0.39 (16/406,769)	1.04 (0.24, 4.55)	1.16 (0.25, 5.29)

SGTF: S gene target failure, here interpreted as a proxy for SARS-CoV-2 variant; CI: confidence interval. Adjusted Cox proportional hazards models control for all variables listed in **Table S2**, with strata for testing date.

¹We define symptomatic hospital admissions as those occurring among cases with respiratory symptom onset dates on or ≤14 days before the date of admission.

Table S13: Association of various clinical and demographic characteristics with symptomatic hospital admission among cases with and without SGTF, 15 December, 2021 to 17 January, 2022.

Characteristic	Measure	Adjusted hazard ratio (95% CI)					
		All cases		SGTF cases (Omicron)		Non-SGTF cases (Delta)	
		Cases tested in outpatient settings	Cases tested in any setting	Cases tested in outpatient settings	Cases tested in any setting	Cases tested in outpatient settings	Cases tested in any setting
Age	<1 year	0.12 (0.04, 0.36)	0.24 (0.12, 0.48)	0.12 (0.03, 0.48)	0.19 (0.07, 0.52)	0.14 (0.02, 1.05)	0.40 (0.14, 1.13)
	1-4 years	0.32 (0.16, 0.61)	0.32 (0.18, 0.55)	0.37 (0.17, 0.79)	0.29 (0.15, 0.58)	0.25 (0.05, 1.27)	0.42 (0.17, 1.08)
	5-9 years	0.27 (0.14, 0.50)	0.31 (0.19, 0.51)	0.28 (0.13, 0.57)	0.38 (0.22, 0.65)	0.34 (0.10, 1.27)	0.22 (0.08, 0.67)
	10-19 years	0.28 (0.19, 0.41)	0.32 (0.24, 0.44)	0.28 (0.19, 0.43)	0.33 (0.23, 0.46)	0.36 (0.16, 0.84)	0.37 (0.20, 0.72)
	20-29 years	0.86 (0.71, 1.04)	0.80 (0.68, 0.95)	0.88 (0.73, 1.08)	0.83 (0.70, 0.99)	0.76 (0.43, 1.35)	0.68 (0.42, 1.14)
	30-39 years	ref.	ref.	ref.	ref.	ref.	ref.
	40-49 years	0.76 (0.64, 0.92)	0.82 (0.70, 0.96)	0.67 (0.54, 0.82)	0.74 (0.62, 0.88)	1.49 (0.94, 2.35)	1.39 (0.94, 2.06)
	50-59 years	0.85 (0.70, 1.03)	0.94 (0.80, 1.11)	0.71 (0.57, 0.88)	0.85 (0.71, 1.03)	2.01 (1.26, 3.15)	1.63 (1.09, 2.43)
	60-69 years	1.34 (1.09, 1.65)	1.37 (1.15, 1.62)	1.03 (0.81, 1.31)	1.08 (0.88, 1.33)	3.54 (2.22, 5.60)	3.13 (2.09, 4.65)
	70-79 years	1.99 (1.55, 2.56)	1.93 (1.56, 2.40)	1.55 (1.16, 2.06)	1.54 (1.21, 1.97)	5.56 (3.23, 9.77)	4.72 (2.94, 7.63)
	≥80 years	2.89 (2.08, 3.99)	2.79 (2.11, 3.71)	2.58 (1.76, 3.77)	2.44 (1.75, 3.42)	5.44 (2.63, 11.4)	5.37 (2.97, 9.78)
Sex	Female	ref.	ref.	ref.	ref.	ref.	ref.
	Male	1.04 (0.92, 1.18)	1.02 (0.92, 1.14)	1.01 (0.88, 1.16)	1.00 (0.89, 1.12)	1.19 (0.91, 1.54)	1.15 (0.92, 1.44)
Race/ethnicity	White	ref.	ref.	ref.	ref.	ref.	ref.
	Black	0.99 (0.79, 1.24)	1.18 (0.98, 1.41)	0.97 (0.76, 1.26)	1.18 (0.97, 1.44)	1.19 (0.70, 1.97)	1.33 (0.89, 1.99)
	Hispanic	1.14 (0.99, 1.33)	1.05 (0.92, 1.19)	1.13 (0.95, 1.35)	1.05 (0.91, 1.22)	1.17 (0.87, 1.60)	1.04 (0.80, 1.35)
	Asian/Pacific islander	1.44 (1.15, 1.80)	1.23 (1.01, 1.48)	1.40 (1.10, 1.79)	1.25 (1.01, 1.55)	1.46 (0.84, 2.49)	0.96 (0.58, 1.59)
	Other, mixed race, or unknown race	0.70 (0.50, 0.98)	0.89 (0.61, 1.04)	0.55 (0.37, 0.84)	0.71 (0.52, 0.97)	1.32 (0.75, 2.29)	1.11 (0.69, 1.79)
Community median income	Per 1-log increase	0.99 (0.85, 1.14)	0.93 (0.83, 1.05)	0.97 (0.83, 1.15)	0.94 (0.82, 1.07)	1.01 (0.72, 1.42)	0.90 (0.69, 1.15)
Cigarette smoking	Never smoker	ref.	ref.	ref.	ref.	ref.	ref.
	Current smoker	0.97 (0.75, 1.24)	0.87 (0.70, 1.10)	0.99 (0.74, 1.32)	0.89 (0.69, 1.14)	0.88 (0.51, 1.51)	0.80 (0.49, 1.28)
	Former smoker	1.01 (0.87, 1.17)	0.98 (0.86, 1.11)	1.04 (0.88, 1.23)	0.96 (0.83, 1.11)	0.93 (0.67, 1.28)	1.07 (0.82, 1.39)
Body mass index	Underweight	0.80 (0.51, 1.27)	0.94 (0.66, 1.33)	0.85 (0.50, 1.45)	0.90 (0.60, 1.36)	0.72 (0.26, 1.96)	1.15 (0.58, 2.26)
	Normal weight	ref.	ref.	ref.	ref.	ref.	ref.
	Overweight	1.35 (1.13, 1.62)	1.18 (1.02, 1.37)	1.37 (1.13, 1.67)	1.20 (1.02, 1.41)	1.38 (0.91, 2.02)	1.17 (0.84, 1.63)
	Obese	1.60 (1.36, 1.90)	1.30 (1.14, 1.50)	1.59 (1.31, 1.92)	1.30 (1.12, 1.52)	1.64 (1.10, 2.41)	1.28 (0.93, 1.77)
Healthcare utilization: outpatient visits	0-4	ref.	ref.	ref.	ref.	ref.	ref.
	5-9	1.89 (1.51, 2.34)	1.69 (1.41, 2.03)	1.98 (1.53, 2.55)	1.79 (1.45, 2.22)	1.52 (0.96, 2.38)	1.32 (0.92, 1.91)
	10-14	2.42 (1.92, 3.06)	2.07 (1.70, 2.51)	2.66 (2.03, 3.44)	2.27 (1.81, 2.84)	1.76 (1.07, 2.88)	1.56 (1.05, 2.33)
	15-19	2.39 (1.85, 3.09)	2.07 (1.68, 2.57)	2.35 (1.76, 3.14)	2.24 (1.75, 2.85)	2.52 (1.51, 4.14)	1.65 (1.07, 2.54)
	≥20-29	3.31 (2.65, 4.13)	2.61 (2.16, 3.16)	3.64 (2.82, 4.71)	2.95 (2.36, 3.68)	2.29 (1.41, 3.71)	1.70 (1.14, 2.52)
Healthcare utilization: ED visits	0	ref.	ref.	ref.	ref.	ref.	ref.
	1	1.38 (1.20, 1.59)	1.37 (1.21, 1.55)	1.31 (1.11, 1.53)	1.32 (1.15, 1.51)	1.61 (1.19, 2.18)	1.55 (1.19, 2.00)
	2	1.52 (1.24, 1.87)	1.43 (1.19, 1.71)	1.38 (1.09, 1.73)	1.34 (1.09, 1.65)	2.12 (1.42, 3.18)	1.84 (1.28, 2.65)
	≥3	1.07 (0.85, 1.35)	1.17 (0.97, 1.41)	1.06 (0.82, 1.37)	1.13 (0.91, 1.40)	1.16 (0.68, 2.02)	1.43 (0.93, 2.19)
Healthcare utilization:							

inpatient admissions	0	ref.	ref.	ref.	ref.	ref.	ref.
	1	11.9 (10.2, 13.9)	14.5 (12.6, 16.7)	13.7 (11.5, 16.4)	16.7 (14.4, 19.4)	7.38 (5.02, 10.8)	8.51 (6.23, 11.6)
	2	12.0 (9.69, 14.8)	14.9 (12.5, 17.8)	14.2 (11.2, 17.8)	17.6 (14.4, 21.3)	6.29 (3.78, 10.5)	8.06 (5.26, 12.3)
	≥3	18.8 (15.7, 22.6)	24.9 (21.4, 29.0)	22.6 (18.5, 27.4)	29.5 (25.0, 34.8)	8.60 (5.14, 14.6)	11.9 (7.87, 17.8)
	Charlson comorbidity index						
	0	ref.	ref.	ref.	ref.	ref.	ref.
	1-2	1.02 (0.87, 1.18)	0.93 (0.81, 1.05)	1.02 (0.87, 1.21)	0.92 (0.80, 1.07)	1.01 (0.72, 1.41)	0.95 (0.71, 1.27)
	3-5	1.39 (1.10, 1.74)	1.17 (0.95, 1.42)	1.41 (1.10, 1.83)	1.21 (0.97, 1.50)	1.33 (0.81, 2.21)	1.09 (0.69, 1.67)
	≥6	1.58 (1.19, 2.08)	1.33 (1.04, 1.69)	1.49 (1.08, 2.05)	1.25 (0.96, 1.65)	2.24 (1.21, 4.11)	1.68 (1.00, 2.80)
Prior SARS-CoV-2 infection	No documented previous infection	ref.	ref.	ref.	ref.	ref.	ref.
	Documented previous infection	0.48 (0.22, 1.07)	0.49 (0.24, 0.97)	0.52 (0.22, 1.26)	0.56 (0.27, 1.19)	0.50 (0.07, 3.92)	0.32 (0.04, 2.31)
COVID-19 vaccination	Unvaccinated	ref.	ref.	ref.	ref.	ref.	ref.
	Ad.26.COVS.S—1 dose	0.48 (0.34, 0.67)	0.61 (0.47, 0.80)	0.54 (0.36, 0.79)	0.67 (0.49, 0.93)	0.39 (0.20, 0.77)	0.52 (0.30, 0.89)
	Ad.26.COVS.S—with any booster dose	0.34 (0.19, 0.62)	0.43 (0.37, 0.50)	0.46 (0.25, 0.84)	0.61 (0.38, 0.99)	0.11 (0.01, 0.76)	0.20 (0.05, 0.84)
	BNT162b2 or mRNA-1273—1 dose	0.51 (0.34, 0.78)	0.59 (0.41, 0.82)	0.46 (0.27, 0.77)	0.59 (0.39, 0.89)	0.69 (0.35, 1.35)	0.61 (0.32, 1.15)
	BNT162b2 or mRNA-1273—2 doses (≥180 days prior)	0.46 (0.32, 0.66)	0.48 (0.43, 0.55)	0.52 (0.44, 0.61)	0.60 (0.52, 0.69)	0.41 (0.16, 1.01)	0.32 (0.13, 0.78)
	BNT162b2 or mRNA-1273—2 doses (91-180 days prior)	0.38 (0.30, 0.49)	0.45 (0.37, 0.56)	0.43 (0.32, 0.56)	0.50 (0.40, 0.64)	0.27 (0.14, 0.54)	0.33 (0.19, 0.58)
	BNT162b2 or mRNA-1273—2 doses (≤90 days prior)	0.41 (0.36, 0.47)	0.43 (0.30, 0.60)	0.51 (0.34, 0.76)	0.48 (0.33, 0.70)	0.17 (0.12, 0.24)	0.23 (0.17, 0.30)
	BNT162b2 or mRNA-1273—3 doses	0.33 (0.28, 0.40)	0.43 (0.37, 0.50)	0.43 (0.35, 0.52)	0.54 (0.46, 0.64)	0.14 (0.08, 0.24)	0.19 (0.12, 0.28)

SGTF: S gene target failure, here interpreted as a proxy for SARS-CoV-2 variant; CI: confidence interval. Adjusted Cox proportional hazards models control for all variables listed in **Table S2**, with strata for testing date. We define symptomatic hospital admissions as those occurring among cases with respiratory symptom onset dates on or ≤14 days before the date of admission.

Table S14: Occurrence of severe clinical outcomes among cases with and without SGTF, stratified by vaccination status, 15 December, 2021 to 17 January, 2022.

Outcome	Vaccination status	Number of cases		Cumulative events over observed follow-up (n of events per 1000 cases)		Hazard ratio (95% CI), Omicron vs. Delta	
		No SGTF (Delta)	SGTF (Omicron)	No SGTF (Delta)	SGTF (Omicron)	Unadjusted	Adjusted
Any hospital admission	Unvaccinated	9,802	65,480	149 (15.2)	316 (4.8)	0.36 (0.29, 0.43)	0.40 (0.33, 0.49)
	Ad.26.COVID.S—1 dose	717	6,874	9 (12.6)	28 (4.1)	0.36 (0.17, 0.76)	0.47 (0.22, 1.00)
	Ad.26.COVID.S—with any booster dose	170	2,329	1 (5.9)	11 (4.7)	0.93 (0.12, 7.31)	0.26 (0.11, 0.59)
	BNT162b2 or mRNA-1273—1 dose	646	6,266	8 (12.4)	15 (2.4)	0.19 (0.08, 0.43)	0.60 (0.23, 1.58)
	BNT162b2 or mRNA-1273—2 doses (≥180 days prior)	7,492	81,266	44 (5.9)	341 (4.2)	0.76 (0.56, 1.04)	0.70 (0.35, 1.40)
	BNT162b2 or mRNA-1273—2 doses (91-180 days prior)	1,600	18,409	9 (5.6)	64 (3.5)	0.69 (0.34, 1.38)	1.05 (0.77, 1.43)
	BNT162b2 or mRNA-1273—2 doses (≤90 days prior)	622	8,548	5 (8.0)	27 (3.2)	0.44 (0.17, 1.13)	0.99 (0.61, 1.61)
	BNT162b2 or mRNA-1273—3 doses	2,256	33,516	16 (7.1)	189 (5.6)	0.73 (0.45, 1.17)	0.59 (0.51, 0.69)
Symptomatic hospital admission ¹	Unvaccinated	9,802	65,480	142 (14.5)	272 (4.2)	0.35 (0.29, 0.43)	0.40 (0.33, 0.49)
	Ad.26.COVID.S—1 dose	717	6,874	9 (12.6)	24 (3.5)	0.36 (0.17, 0.76)	0.47 (0.22, 1.00)
	Ad.26.COVID.S—with any booster dose	170	2,329	1 (5.9)	10 (4.3)	0.94 (0.12, 7.28)	0.26 (0.11, 0.59)
	BNT162b2 or mRNA-1273—1 dose	646	6,266	7 (10.8)	14 (2.2)	0.19 (0.08, 0.43)	0.59 (0.22, 1.53)
	BNT162b2 or mRNA-1273—2 doses (≥180 days prior)	7,492	81,266	41 (5.5)	308 (3.8)	0.75 (0.55, 1.03)	0.69 (0.34, 1.39)
	BNT162b2 or mRNA-1273—2 doses (91-180 days prior)	1,600	18,409	8 (5.0)	59 (3.2)	0.68 (0.34, 1.37)	1.03 (0.76, 1.41)
	BNT162b2 or mRNA-1273—2 doses (≤90 days prior)	622	8,548	5 (1.0)	22 (2.6)	0.42 (0.16, 1.10)	0.97 (0.60, 1.58)
	BNT162b2 or mRNA-1273—3 doses	2,256	33,516	13 (5.8)	169 (5.0)	0.72 (0.44, 1.15)	0.59 (0.51, 0.68)
ICU admission	Unvaccinated	9,802	65,480	20 (2.0)	22 (0.3)	0.21 (0.11, 0.39)	0.34 (0.17, 0.66)
	Any COVID-19 vaccination	13,503	157,208	4 (0.3)	28 (0.2)	0.68 (0.24, 1.95)	0.95 (0.33, 2.76)
Mechanical ventilation	Unvaccinated	9,802	65,480	16 (1.6)	12 (0.2)	0.14 (0.06, 0.31)	0.24 (0.12, 0.48)
	Any COVID-19 vaccination	13,503	157,208	1 (0.1)	12 (0.1)	1.18 (0.15, 8.95)	1.50 (0.56, 3.99)
Death	Unvaccinated	9,802	65,480	12 (1.2)	5 (0.1)	0.07 (0.03, 0.22)	0.14 (0.07, 0.28)
	Any COVID-19 vaccination	13,503	157,208	7 (0.5)	12 (0.1)	0.16 (0.06, 0.42)	0.25 (0.09, 0.70)

SGTF: S gene target failure, here interpreted as a proxy for SARS-CoV-2 variant; CI: confidence interval. Adjusted Cox proportional hazards models control for all variables listed in **Table S2**, with strata for testing date. Estimates are presented visually in **Figure 3** and **Figure S3**.

¹We define symptomatic hospital admissions as those occurring among cases with respiratory symptom onset dates on or ≤14 days before the date of admission.

Table S15: Dates of change in slopes for Cox proportional hazards models relating testing date to risk of severe clinical outcomes.

Endpoint	Quantile	Changepoint date (95% CI)
Any hospital admission	Point estimate	22 December, 2021
	25-75%ile	20 December, 2021 to 24 December, 2021
	2.5-97.5%ile	13 December, 2021 to 3 January, 2022
Symptomatic hospital admission	Point estimate	23 December, 2021
	25-75%ile	21 December, 2021 to 24 December, 2021
	2.5-97.5%ile	13 December, 2021 to 4 January, 2022
ICU admission	Point estimate	13 December, 2021
	25-75%ile	7 December, 2021 to 17 December, 2021
	2.5-97.5%ile	19 November, 2021 to 3 January, 2022
Mortality	Point estimate	8 December, 2021
	25-75%ile	4 December, 2021 to 11 December, 2021
	2.5-97.5%ile	21 November, 2021 to 28 December, 2021

CI: Confidence interval. Adjusted Cox proportional hazards models fitted with 0, 1, or 2 changepoints (allowed for each date from 15 November, 2021 to 10 January, 2022) were sampled according to posterior weights. Daily adjusted hazards (controlling for all variables listed in **Table S2**) are illustrated in the inset panels to **Figure 4**.

Table S16: Disposition at completion of hospitalization among patients with completed hospital stays.

Discharge disposition	Number of cases (%)			
	15 December, 2021 to 17 January, 2022		3 February to 17 March, 2022	
	No SGTF (Delta)	SGTF (Omicron)	No SGTF (BA.2)	SGTF (BA.1*)
	<i>N</i> =208	<i>N</i> =703	<i>N</i> =23	<i>N</i> =146
Home (self-care)	138 (66.3)	582 (82.8)	20 (87.0)	124 (84.9)
Home with skilled care provision	22 (10.6)	36 (5.1)	2 (8.7)	8 (5.5)
Discharged against medical advice	4 (1.9)	1 (0.1)	0 (0.0)	2 (1.4)
SNF, Residential facility, or rehabilitation facility	2 (1.0)	3 (0.4)	0 (0.0)	2 (1.4)
Other acute inpatient hospital	2 (1.0)	2 (0.3)	0 (0.0)	1 (0.7)
Hospice care/in-hospital death	2 (1.0)	3 (0.4)	0 (0.0)	0 (0.0)
Final disposition not recorded	38 (18.3)	76 (10.8)	1 (4.3)	9 (6.2)

SGTF: S gene target failure. Cases in the table are subset to those tested in outpatient settings and admitted within the indicated date ranges, with symptoms onset on or ≤14 days before this date.

Table S17: Association of SGTF with time to completion of hospital stay among outpatient-diagnosed cases with symptoms onset on or before admission date, 15 December, 2021 to 17 January, 2022 and 3 February to 17 March, 2022.

Comparison and period	Hazard ratio (95% CI)	
	Unadjusted	Adjusted
Omicron (SGTF) vs. Delta (No SGTF) 15 December, 2021 to 17 January, 2022	1.46 (1.20, 1.77)	1.24 (0.99, 1.57)
BA.2 (No SGTF) vs. BA.1* (SGTF) 3 February to 17 March, 2022	1.02 (0.61, 1.70)	0.95 (0.41, 2.22)

SGTF: S gene target failure, here interpreted as a proxy for SARS-CoV-2 variant; CI: confidence interval. Adjusted Cox proportional hazards models control for all variables listed in **Table S2**, with strata for admission date.

Table S18: Attributes of outpatient cases with samples processed using the ThermoFisher TaqPath COVID-19 Combo Kit or other assays, 1 November, 2021 to 17 March, 2022.

Characteristic	Number of cases (%)	
	ThermoFisher TaqPath COVID-19 combo kit N=329,195	Other assay N=60,701
Age ¹		
<1 year	2,449 (0.7)	1,024 (1.7)
1-4 years	1,024 (1.7)	11,381 (3.5)
5-9 years	19,606 (6.0)	2,724 (4.5)
10-19 years	42,306 (12.9)	6,326 (10.4)
20-29 years	50,660 (15.4)	8,250 (13.6)
30-39 years	64,575 (19.6)	10,476 (17.3)
40-49 years	54,743 (16.6)	8,678 (14.3)
50-59 years	43,474 (13.2)	7,840 (12.9)
60-69 years	25,467 (7.7)	5,356 (8.8)
70-79 years	10,168 (3.1)	3,071 (5.1)
≥80 years	2,888 (0.9)	1,762 (2.9)
Sex		
Female	181,095 (55.0)	34,740 (57.2)
Male	148,100 (42.8)	25,961 (42.8)
Race/ethnicity		
White, non-Hispanic	77,178 (23.4)	12,424 (20.5)
Black, non-Hispanic	23,977 (7.3)	6,962 (11.5)
Hispanic	164,253 (49.9)	28,954 (47.7)
Asian/Pacific Islander	33,124 (10.1)	5,088 (8.4)
Other, mixed race, or unknown race	30,663 (9.3)	7,723 (12.0)
Community median income ¹		
<\$50,000	51,236 (15.8)	13,141 (22.6)
\$50,000-\$99,999	197,975 (61.1)	34,070 (58.5)
\$100,000-149,999	66,279 (20.4)	9,440 (16.2)
≥\$150,000	8,738 (2.7)	1,587 (2.7)
Cigarette smoking ¹		
Never smoker	198,294 (81.4)	34,834 (78.5)
Current smoker	10,138 (4.2)	2,255 (5.1)
Former smoker	35,069 (14.4)	7,296 (16.4)
Body mass index ¹		
Underweight (<18.5)	24,043 (9.7)	3,847 (7.9)
Normal weight (18.5-24.9)	60,702 (24.4)	11,706 (24.2)
Overweight (25.0-29.9)	69,807 (28.1)	13,873 (28.7)
Obese (≥30)	94,123 (37.8)	18,992 (39.2)
Healthcare utilization: outpatient visits		
0-4	114,208 (34.7)	19,299 (31.8)
5-9	89,891 (27.3)	14,958 (24.6)
10-14	48,057 (14.6)	8,926 (14.7)
15-19	27,175 (8.3)	5,405 (8.9)
≥20	49,864 (15.1)	12,113 (20.0)
Healthcare utilization: ED visits		
0	269,559 (81.9)	35,800 (59.0)
1	42,401 (12.9)	14,833 (24.4)
2	10,660 (3.2)	5,227 (8.6)
≥3	6,575 (2.0)	4,841 (8.0)
Healthcare utilization: inpatient admissions		
0	319,297 (97.0)	58,302 (96.0)
1	5,333 (1.6)	1,248 (2.1)
2	2,215 (0.7)	516 (0.9)
≥3	2,350 (0.7)	635 (1.0)
Charlson comorbidity index		
0	265,307 (80.6)	45,474 (74.9)
1-2	52,570 (16.0)	10,817 (17.8)
3-5	8,446 (2.6)	2,919 (4.8)
≥6	2,872 (0.9)	1,491 (2.5)
Prior SARS-CoV-2 infection ²		
Documented previous infection	1,606 (0.5)	336 (0.6)
COVID-19 vaccination		
Unvaccinated	106,322 (32.3)	21,188 (34.9)
Ad.26.COVID.S—1 dose	9,850 (3.0)	2,052 (3.4)
Ad.26.COVID.S—with any booster dose	3,449 (1.0)	740 (1.2)
BNT162b2 or mRNA-1273—1 dose	9,069 (2.8)	1,712 (2.8)
BNT162b2 or mRNA-1273—2 doses (≥180 days prior)	110,296 (33.5)	19,017 (31.3)
BNT162b2 or mRNA-1273—2 doses (91-180 days prior)	26,057 (7.9)	4,534 (7.5)
BNT162b2 or mRNA-1273—2 doses (≤90 days prior)	12,329 (3.7)	2,142 (3.5)
BNT162b2 or mRNA-1273—3 doses	51,823 (15.7)	9,316 (15.3)
Symptoms		
Any new-onset acute respiratory symptoms on or before testing date	254,242 (77.2)	48,039 (79.1)
Days since symptoms onset, among symptomatic cases, mean (±SD)	3.9 (±3.5)	4.1 (±3.9)

Subsequent outcomes			
	Any hospital admission	2,428 (0.7)	1,058 (1.7)
	Symptomatic hospital admission	2,181 (0.7)	1,006 (1.7)

¹Multiple imputation was used to address missing data; numbers may not add to column totals where missing values occur. The number of missing observations for each variable is specified in **Table S21**.

²Previous infection defined by any positive test result or diagnosis ≥ 90 days prior to the date of the current test.

Table S19: Onset of acute respiratory symptoms on or before dates of testing and hospital admission.

Case sample	Number of cases with symptom onset by indicated time (%)	
	No SGTF	SGTF
All cases—onset on or before testing date	<i>15 December, 2021 to 17 January, 2022</i>	
	<i>N=23,517</i>	<i>N=224,065</i>
	<i>19,179 (81.6)</i>	<i>174,528 (77.9)</i>
	<i>3 February to 17 March, 2022</i>	
	<i>N=1,937</i>	<i>N=12,892</i>
	<i>1,573 (81.2)</i>	<i>9,102 (70.6)</i>
Cases tested in outpatient settings—onset on or before testing date	<i>15 December, 2021 to 17 January, 2022</i>	
	<i>N=23,305</i>	<i>N=222,688</i>
	<i>19,005 (81.5)</i>	<i>173,575 (77.9)</i>
	<i>3 February to 17 March, 2022</i>	
	<i>N=1,905</i>	<i>N=12,756</i>
	<i>1,546 (81.2)</i>	<i>9,014 (70.7)</i>
Hospitalized cases—onset on or before hospital admission date	<i>15 December, 2021 to 17 January, 2022</i>	
	<i>N=343</i>	<i>N=1,441</i>
	<i>301 (87.8)</i>	<i>1,061 (73.6)</i>
	<i>3 February to 17 March, 2022</i>	
	<i>N=49</i>	<i>N=224</i>
	<i>41 (83.7)</i>	<i>179 (79.9)</i>

SGTF: S gene target failure, here interpreted as a proxy for SARS-CoV-2 variant.

Symptoms data were collected from free-text fields of patient EHRs, including data from clinical notes and from responses to questionnaires addressing symptoms in the 14 days before testing which all patients must complete to receive a test.

Table S20: Attributes of outpatient cases with and without symptoms at the time of outpatient testing, 1 November, 2021 to 17 March, 2022.

Characteristic	Number of cases (%)	
	Symptoms onset on or before testing date	No symptoms by date of test
	N=308,720	N=88,606
Age ¹		
<1 year	2,950 (1.0)	585 (0.7)
1-4 years	9,929 (3.2)	3,967 (4.5)
5-9 years	13,997 (4.5)	8,418 (9.5)
10-19 years	33,085 (10.7)	15,791 (17.8)
20-29 years	50,055 (16.2)	9,755 (11.0)
30-39 years	63,011 (20.4)	13,156 (14.8)
40-49 years	51,922 (16.8)	12,239 (13.8)
50-59 years	41,244 (13.4)	10,999 (12.4)
60-69 years	24,186 (7.8)	7,633 (8.6)
70-79 years	10,309 (3.3)	3,845 (4.3)
≥80 years	4,217 (1.4)	1,221 (1.4)
Sex		
Female	174,230 (56.4)	46,065 (52.0)
Male	134,490 (43.6)	42,541 (48.0)
Race/ethnicity		
White, non-Hispanic	72,267 (23.4)	19,179 (21.6)
Black, non-Hispanic	22,973 (7.4)	8,913 (10.1)
Hispanic	153,717 (49.8)	42,813 (48.3)
Asian/Pacific Islander	29,639 (9.6)	9,069 (10.2)
Other, mixed race, or unknown race	30,124 (9.8)	8,632 (9.7)
Community median income ¹		
<\$50,000	50,148 (16.6)	15,685 (18.0)
\$50,000-\$99,999	184,365 (61.0)	51,811 (59.5)
\$100,000-149,999	59,993 (19.8)	16,891 (19.4)
≥\$150,000	7,831 (2.6)	2,665 (3.1)
Cigarette smoking ¹		
Never smoker	184,224 (80.4)	52,824 (82.3)
Current smoker	10,021 (4.4)	2,682 (4.2)
Former smoker	35,026 (15.3)	8,669 (13.5)
Body mass index ¹		
Underweight (<18.5)	18,837 (7.9)	9,308 (14.2)
Normal weight (18.5-24.9)	56,445 (23.7)	17,518 (26.6)
Overweight (25.0-29.9)	67,792 (28.5)	17,912 (27.2)
Obese (≥30)	95,181 (39.9)	21,037 (32.0)
Healthcare utilization: outpatient visits		
0-4	101,333 (32.8)	33,993 (38.4)
5-9	82,114 (26.6)	23,961 (27.0)
10-14	45,891 (14.9)	12,086 (13.6)
15-19	26,869 (8.7)	6,556 (7.4)
≥20	52,513 (17.0)	12,010 (13.6)
Healthcare utilization: ED visits		
0	235,765 (76.4)	73,796 (83.3)
1	48,124 (15.6)	10,708 (12.1)
2	14,097 (4.6)	2,514 (2.8)
≥3	10,734 (3.5)	1,588 (1.8)
Healthcare utilization: inpatient admissions		
0	296,595 (96.1)	85,922 (97.0)
1	6,340 (2.1)	1,365 (1.5)
2	2,663 (0.9)	584 (0.7)
≥3	3,122 (1.0)	735 (0.8)
Charlson comorbidity index		
0	243,602 (78.9)	71,408 (80.6)
1-2	51,309 (16.6)	13,575 (15.3)
3-5	9,720 (3.1)	2,644 (3.0)
≥6	4,089 (1.3)	979 (1.1)
Prior SARS-CoV-2 infection ²		
No documented previous infection	307,191 (99.5)	88,159 (99.5)
Documented previous infection	1,529 (0.5)	447 (0.5)
COVID-19 vaccination		
Unvaccinated	97,234 (31.5)	33,533 (37.8)
Ad.26.COVID.S—1 dose	10,023 (3.2)	2,154 (2.4)
Ad.26.COVID.S—with any booster dose	3,399 (1.1)	862 (1.0)
BNT162b2 or mRNA-1273—1 dose	8,318 (2.7)	2,665 (3.0)
BNT162b2 or mRNA-1273—2 doses (≥180 days prior)	107,654 (34.9)	23,622 (26.7)
BNT162b2 or mRNA-1273—2 doses (91-180 days prior)	24,124 (7.8)	6,830 (7.7)
BNT162b2 or mRNA-1273—2 doses (≤90 days prior)	10,455 (3.4)	4,166 (4.7)
BNT162b2 or mRNA-1273—3 doses	47,513 (15.4)	14,774 (16.7)

¹Multiple imputation was used to address missing data; numbers may not add to column totals where missing values occur. The number of missing observations for each variable is specified in **Table S21**.

²Previous infection defined by any positive test result or diagnosis ≥90 days prior to the date of the current test.

Table S21: Summary of missing data.

Variable	Missing observations, <i>n</i> (%) among cases tested in outpatient settings	
	Full analysis population ¹	Population enrolled ≥1 year
	<i>N</i> =329,195	<i>N</i> =283,453
Age	2,535 (0.8)	755 (0.3)
Sex	1,057 (0.3)	755 (0.3)
Community median income	6,024 (1.8)	1,014 (0.4)
History of cigarette smoking	86,751 (26.3)	64,961 (22.9)
BMI	81,577 (24.7)	62,826 (22.1)
Any missing observation	107,870 (32.7)	81,923 (28.8)
Total missing observations, across all covariates analyzed	188,514 (3.8)	137,861 (3.2)

¹The primary analysis population includes outpatient-tested cases whose samples were processed using the ThermoFisher TaqPath COVID-19 combo kit.

Table S22: Association of imputed variables with symptomatic hospital admission endpoint across differing analysis strategies.

Characteristic	Case population ¹	Primary analysis: Adjusted hazard ratio (95% CI)	Complete case analysis: Adjusted hazard ratio (95% CI)	Participants enrolled ≥1 year: Adjusted hazard ratio (95% CI)
Age	<1 year	0.12 (0.04, 0.36)	--	--
	1-4 year	0.32 (0.16, 0.61)	0.34 (0.12, 0.94)	0.28 (0.13, 0.60)
	5-9 years	0.27 (0.14, 0.50)	0.44 (0.23, 0.87)	0.24 (0.12, 0.48)
	10-19 years	0.28 (0.19, 0.41)	0.31 (0.21, 0.48)	0.29 (0.20, 0.43)
	20-29 years	0.86 (0.71, 1.04)	0.90 (0.73, 1.10)	0.84 (0.68, 1.04)
	30-39 years	ref.	ref.	ref.
	40-49 years	0.76 (0.64, 0.92)	0.70 (0.57, 0.86)	0.78 (0.64, 0.96)
	50-59 years	0.85 (0.70, 1.03)	0.79 (0.64, 0.98)	0.90 (0.73, 1.11)
	60-69 years	1.34 (1.09, 1.65)	1.19 (0.95, 1.49)	1.44 (1.15, 1.79)
	70-79 years	1.99 (1.55, 2.56)	1.79 (1.37, 2.32)	2.01 (1.55, 2.62)
≥80 years	2.89 (2.08, 3.99)	2.38 (1.68, 3.39)	2.88 (2.04, 4.07)	
Community median income (continuous) ²	Per 1-log increase	0.99 (0.85, 1.14)	1.04 (0.88, 1.23)	1.01 (0.86, 1.18)
Community median income (factorized) ²	<\$50,000	0.95 (0.80, 1.13)	0.94 (0.79, 1.12)	0.95 (0.80, 1.13)
	\$50,000-\$99,999	ref.	ref.	ref.
	\$100,000-\$149,999	0.88 (0.75, 1.04)	0.91 (0.77, 1.08)	0.88 (0.74, 1.04)
	≥\$150,000	0.64 (0.39, 1.04)	0.72 (0.45, 1.15)	0.65 (0.40, 1.05)
Cigarette smoking ²	Never smoker	ref.	ref.	ref.
	Current smoker	0.97 (0.75, 1.24)	1.09 (0.82, 1.45)	0.97 (0.73, 1.30)
	Former smoker	1.01 (0.87, 1.17)	1.06 (0.91, 1.24)	1.04 (0.89, 1.22)
Body mass index ²	Underweight (<18.5)	0.80 (0.51, 1.27)	0.72 (0.39, 1.33)	0.91 (0.56, 1.49)
	Normal weight (18.5-24.9)	ref.	ref.	ref.
	Overweight (25.0-29.9)	1.35 (1.13, 1.62)	1.47 (1.21, 1.79)	1.33 (1.10, 1.61)
	Obese (≥30)	1.60 (1.36, 1.90)	1.71 (1.42, 2.07)	1.61 (1.34, 1.94)

CI: confidence interval. Adjusted Cox proportional hazards models control for all variables listed in **Table S2**, with strata for testing date

¹The primary analysis population includes outpatient-tested cases whose samples were processed using the ThermoFisher TaqPath COVID-19 combo kit.

²Primary analyses addressed community median household income as a continuous variable; we present the factorized version (broken down by increments of \$50,000/year) to further illustrate similarity of effect estimates across the analysis strategies.

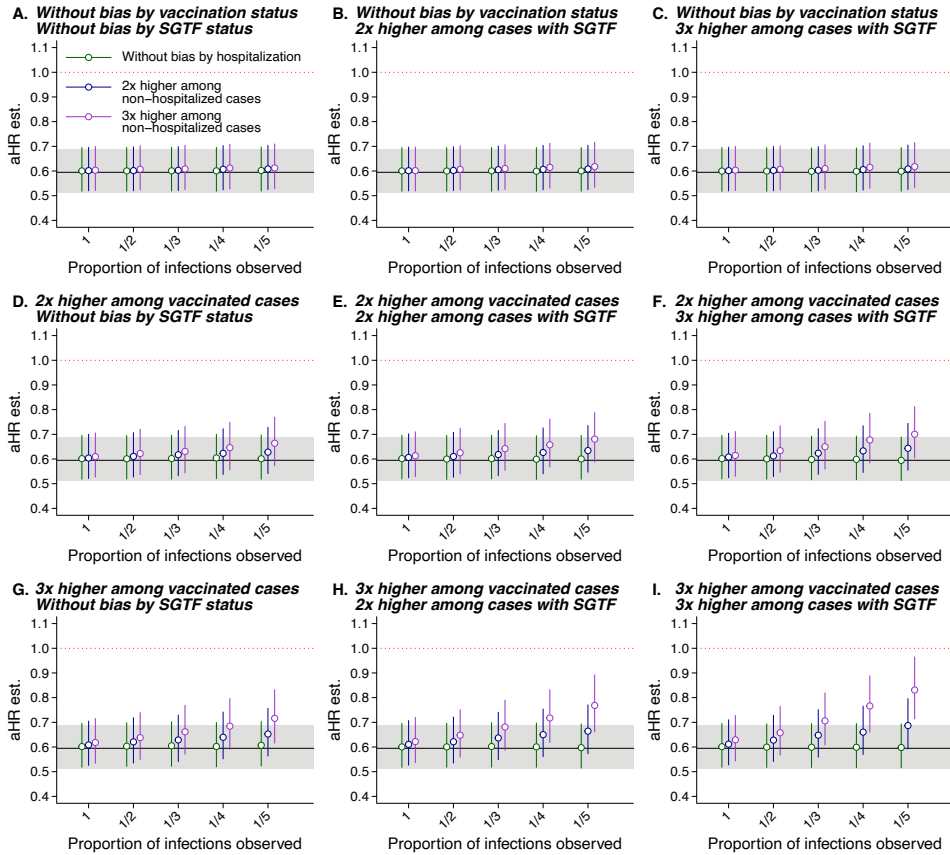


Figure S1: Estimates of the adjusted hazard ratio (aHR) of any hospital admission under scenarios of differential unobserved prior infection prevalence across case strata. We illustrate values of the aHR of any hospital admission among outpatient diagnosed cases with Omicron vs. Delta infection, estimated in analyses allowing for differing levels of prior infection prevalence according to their infecting variant, outcome (hospital admission or no hospital admission), and history of vaccination. Panels indicate the fold elevation in infection prevalence applied to each stratum over a baseline proportion of infections assumed to be unascertained on the x-axis for unvaccinated cases with Delta variant infection who were hospitalized (highest-risk stratum). Horizontal lines at aHR=0.59 and accompanying gray shaded areas delineate the point estimate and 95% confidence interval from primary analysis models.

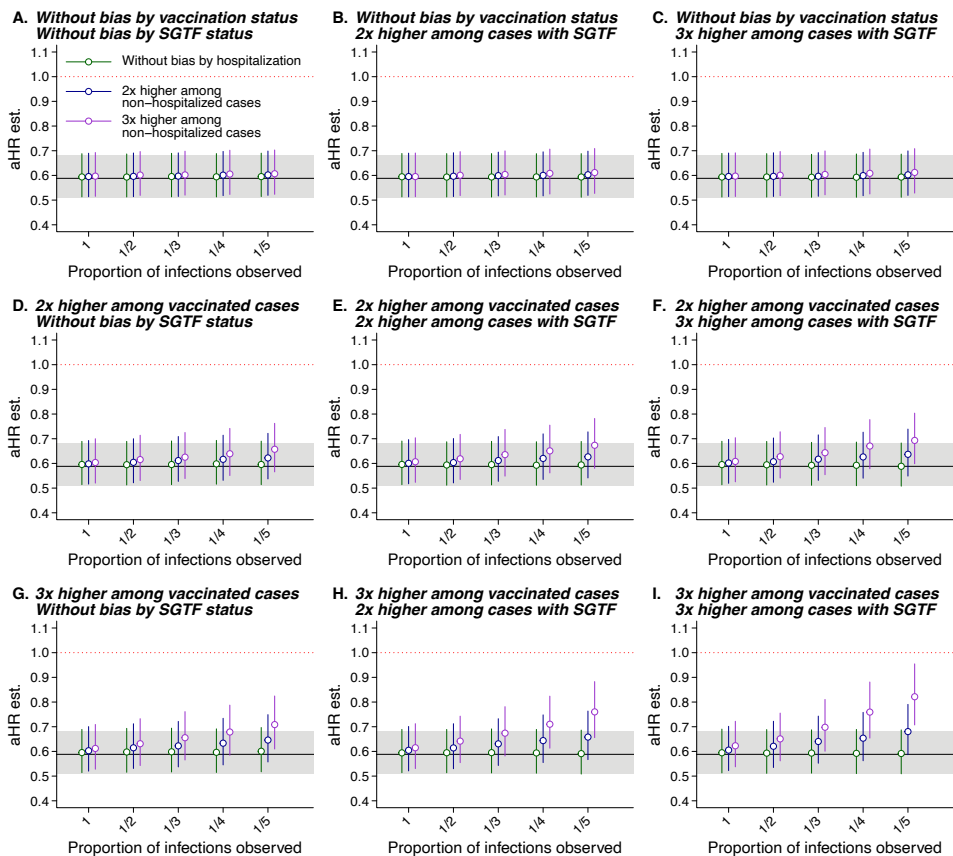


Figure S2: Estimates of the adjusted hazard ratio (aHR) of symptomatic hospital admission under scenarios of differential unobserved prior infection prevalence across case strata. We illustrate values of the aHR of any hospital admission among outpatient diagnosed cases with Omicron vs. Delta infection, estimated in analyses allowing for differing levels of prior infection prevalence according to their infecting variant, outcome (symptomatic hospital admission or no symptomatic hospital admission), and history of vaccination. Panels indicate the fold elevation in infection prevalence applied to each stratum over a baseline proportion of infections assumed to be unascertained on the x-axis for unvaccinated cases with Delta variant infection who were hospitalized (highest-risk stratum). Horizontal lines at $aHR=0.59$ and accompanying gray shaded areas delineate the point estimate and 95% confidence interval from primary analysis models.

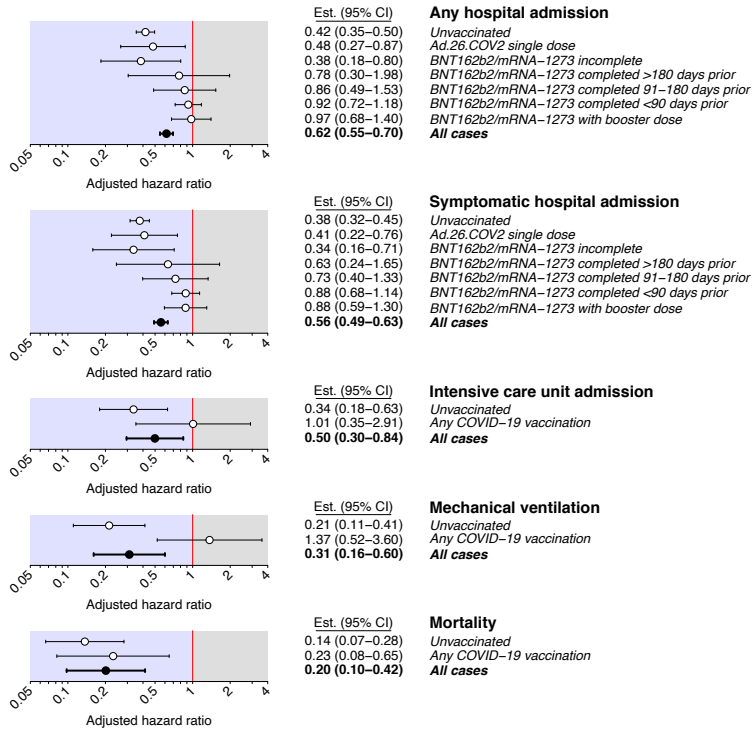


Figure S3: Adjusted hazard ratios of severe clinical endpoints associated with Omicron variant infection, without restriction by diagnosis setting. Points and lines denote estimates and accompanying 95% confidence intervals for the adjusted hazard ratio of each endpoint, comparing cases with Omicron versus Delta variant infection, in case strata defined by history of COVID-19 vaccination. Analyses are restricted to individuals tested diagnosed by RT-PCR testing using the ThermoFisher TaqPath COVID-19 combo kit, in contrast to **Figure 3** which further limits analyses to cases diagnosed in outpatient settings. Adjusted hazard ratios are estimated using Cox proportional hazards regression models, controlling for covariates listed in **Table S2** and defining strata for testing date.

Proportion of cases identified at admission

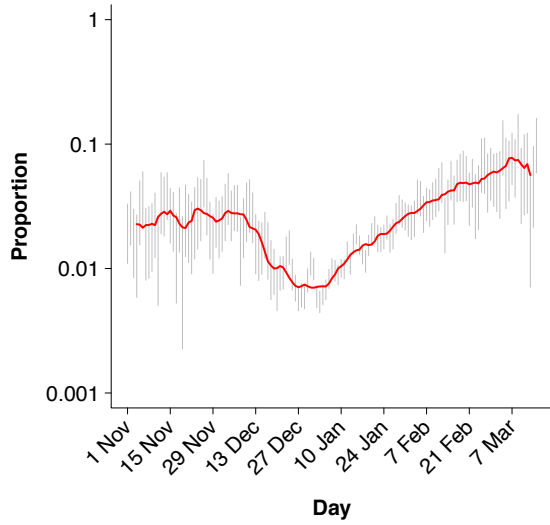


Figure S4: Changes in the proportion of cases ascertained on or after the date of hospital admission. We illustrate day-specific estimates of the proportion of cases ascertained on or after the hospital admission date with 95% confidence intervals generated by bootstrap sampling (grey lines) as well as the 7-day moving average (red line).