Open Forum Infectious Diseases

MAJOR ARTICLE

Association Between SARS-CoV-2 Variants and Frequency of Acute Symptoms: Analysis of a Multi-institutional Prospective Cohort Study—December 20, 2020—June 20, 2022

Ralph C. Wang,[1,a] Michael Gottlieb,[2,a] Juan Carlos C. Montoy,[1] Robert M. Rodriguez,[1] Huihui Yu,[3] Erica S. Spatz,[3] Christopher W. Chandler,[4] Joann G. Elmore,[4,5] Paavali A. Hannikainen,[6] Anna Marie Chang,[6] Mandy Hill,[7] Ryan M. Huebinger,[7] Ahamed H. Idris,[8] Katherine Koo,[9] Shu-Xia Li,[3] Samuel McDonald,[8] Graham Nichol,[10] Kelli N. O'Laughlin,[11] Ian D. Plumb,[12] Michelle Santangelo,[13] Sharon Saydah,[12] Kari A. Stephens,[14] Arjun K. Venkatesh,[3,15,b] and Robert A. Weinstein,[9,b] for the Innovative Support for Patients with SARS-CoV-2 Infections Registry (INSPIRE) Group[c]

[1]Department of Emergency Medicine, University of California San Francisco, San Francisco, California, USA, [2]Department of Emergency Medicine, Rush University Medical Center, Chicago, Illinois, USA, [3]Center for Outcomes Research and Evaluation, Section of Cardiovascular Medicine, Yale School of Medicine, New Haven, Connecticut, USA, [4]Division of General Internal Medicine and Health Services Research, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, California, USA, [5]Department of Health Policy and Management, Fielding School of Public Health, University of California Los Angeles, Los Angeles, California, USA, [6]Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, Pennsylvania, USA, [7]Department of Emergency Medicine, UTHealth Houston, Houston, Texas, USA, [8]Department of Emergency Medicine, University of Texas Southwestern Medical Center, Dallas, Texas, USA, [9]Department of Medicine, Division of Infectious Diseases, Rush University Medical Center, Chicago, Illinois, USA, [10]Departments of Medicine and Emergency Medicine, University of Washington, Seattle, Washington, USA, [11]Departments of Emergency Medicine and Global Health, University of Washington, Seattle, Washington, USA, [12]Centers for Disease Control and Prevention, National Center for Immunizations and Respiratory Diseases, Atlanta, Georgia, USA, [13]Division of Infectious Diseases, Department of Medicine, Rush University Medical Center, Chicago, Illinois, USA, [14]Departments of Family Medicine and Biomedical Informatics & Medical Education, University of Washington, Seattle, Washington, USA, and [15]Department of Emergency Medicine, Yale School of Medicine, New Haven, Connecticut, USA

Background. While prior work examining severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants of concern focused on hospitalization and death, less is known about differences in clinical presentation. We compared the prevalence of acute symptoms across pre-Delta, Delta, and Omicron.

Methods. We conducted an analysis of the Innovative Support for Patients with SARS-CoV-2 Infections Registry (INSPIRE), a cohort study enrolling symptomatic SARS-CoV-2-positive participants. We determined the association between the pre-Delta, Delta, and Omicron time periods and the prevalence of 21 coronavirus disease 2019 (COVID-19) acute symptoms.

Results. We enrolled 4113 participants from December 2020 to June 2022. Pre-Delta vs Delta vs Omicron participants had increasing sore throat (40.9%, 54.6%, 70.6%; $P < .001$), cough (50.9%, 63.3%, 66.7%; $P < .001$), and runny noses (48.9%, 71.3%, 72.9%; $P < .001$). We observed reductions during Omicron in chest pain (31.1%, 24.2%, 20.9%; $P < .001$), shortness of breath (42.7%, 29.5%, 27.5%; $P < .001$), loss of taste (47.1%, 61.8%, 19.2%; $P < .001$), and loss of smell (47.5%, 55.6%, 20.0%; $P < .001$). After adjustment, those infected during Omicron had significantly higher odds of sore throat vs pre-Delta (odds ratio [OR], 2.76; 95% CI, 2.26–3.35) and Delta (OR, 1.96; 95% CI, 1.69–2.28).

Conclusions. Participants infected during Omicron were more likely to report symptoms of common respiratory viruses, such as sore throat, and less likely to report loss of smell and taste.

Trial registration. NCT04610515.

Keywords. COVID-19; COVID-19 symptoms; SARS-COV-2; variants of concern.

Received 05 April 2023; editorial decision 08 May 2023; accepted 22 May 2023; published online 23 May 2023

[a]Co-first authors, equal contribution.

[b]Co-last authors, equal contribution.

[c]Study Group Team Members are listed in the Acknowledgments.

Correspondence: Ralph C. Wang, MD, MAS, 505 Parnassus Avenue, L-126, San Francisco, CA 94143 (ralph.wang@ucsf.edu); or Michael Gottlieb, MD, 1750 West Harrison Street, Suite 108 Kellogg, Chicago, IL 60612 (michaelgottliebmd@gmail.com).

Open Forum Infectious Diseases®

https://doi.org/10.1093/ofid/ofad275

In November 2020, the Centers for Disease Control and Prevention (CDC) established a national surveillance program for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants using genomic sequencing to track SARS-CoV-2 lineages [1–6]. The CDC identified 6 major variants of concern (VOCs): Alpha, Beta, Gamma, Delta, Epsilon, and Omicron [2, 4]. These VOCs generally had increased transmissibility and immune escape characteristics compared with the ancestral lineage [4, 7]. The Alpha, Delta, and Omicron variants have resulted in the greatest clinical burden of disease, including surges in infections, hospitalizations, and deaths [8]. Omicron (B.1.1.529), the dominant variant at

the time of writing, includes a number of sublineages, such as BA.1, BA.2, BA.4, and BA.5 [8, 9]. Studies comparing pre-Delta with Delta cases reported increased hospitalization rates during the Delta period [8], and subsequent studies reported lower risk of hospitalization or death among those infected with Omicron compared with the Delta variant [10–13]. Despite milder infections on average with the Omicron variant, rapid transmission resulted in a larger absolute number of deaths [9, 14].

While most prior work comparing variants has focused on differences in death and hospitalization, less is known about associated clinical features that may have implications for diagnosis, transmission, and morbidity [15]. Coronavirus disease 2019 (COVID-19) can present with a wide array of symptoms, including fever, cough, fatigue, shortness of breath, vomiting or diarrhea, and loss of taste or smell [16–18]. In addition, patients with COVID-19 may have symptoms ranging from mild or none to severe illness [19]. Initial CDC case definitions were limited to 3 typical (fever, cough, and shortness of breath) and 4 gastrointestinal (diarrhea, vomiting, nausea, and abdominal pain) symptoms suggestive of COVID-19 [20], while recent CDC case definitions included up to 18 symptoms, reflecting an evolving understanding of COVID-19 and epidemiologic evolution [21]. Prior studies from the United Kingdom found that symptom profiles differed by variant, including a higher prevalence of sore throat and rhinorrhea from Omicron and a lower prevalence of shortness of breath, loss of smell, and loss of taste compared with previous variants [15]. Understanding changes in the clinical presentation of COVID-19 VOCs in the United States can help guide clinicians and public health officials managing and monitoring SARS-CoV-2 infections.

Using data from the Innovative Support for Patients with SARS-CoV-2 Infections Registry (INSPIRE), a multicenter prospective study designed to assess the long-term symptoms of symptomatic adult patients tested for SARS-CoV-2, we sought to characterize the prevalence of and risk factors for acute symptoms across 3 major COVID-19 viral variant time periods in the United States: pre-Delta, Delta, and Omicron.

METHODS

Study Design and Setting

This analysis uses data collected prospectively as part of the INSPIRE Registry, a multisite prospective longitudinal cohort enrolling symptomatic SARS-CoV-2-positive and SARS-CoV-2-negative participants to determine long-term sequelae. The INSPIRE study protocol has been described previously [22]. Briefly, participants were recruited at the point of testing (eg, tent/drive-up testing site, ambulatory site, emergency department, or hospital) by 1 of 8 institutions across the United States: Rush University (Chicago, Illinois), Yale University (New Haven, Connecticut), the University of Washington (Seattle, Washington), Thomas Jefferson University (Philadelphia, Pennsylvania), the University of Texas Southwestern (Dallas, Texas), UTHealth Houston (Houston, Texas), the University of California, San Francisco (San Francisco, California), and the University of California, Los Angeles (Los Angeles, California). In addition, sites recruited participants through a study website and other methods, allowing for virtual enrollment across the entire United States. Study participants completed a baseline survey. A cloud-based platform (Hugo Health; Hugo Health, LLC, Guilford, CT, USA) enabled participants to share health information including patient-reported outcomes in surveys, test results, and electronic health records (EHRs). We followed the Strengthening of Reporting of Observational Studies in Epidemiology guidelines [23].

Patient Consent

All participants provided written informed consent (see 45 C.F.R. part 46; 21 C.F.R. part 56). This study was reviewed and approved by the local institutional review boards at all 8 sites (Rush University, Yale University, the University of Washington, Thomas Jefferson University, the University of Texas Southwestern, UTHealth Houston, the University of California, San Francisco, and the University of California, Los Angeles).

Study Participants

Participants were enrolled if they were adults (age ≥18 years), fluent in English or Spanish, reported symptoms suggestive of acute SARS-CoV-2 infection, and tested for SARS-CoV-2 with any Food and Drug Administration–approved diagnostic test within 42 days before enrollment. Individuals were ineligible for recruitment if they were unable to provide informed consent, unable to confirm the result of a diagnostic test for SARS-CoV-2 infection, did not have access to an internet-enabled device or computer that would allow for digital participation in the study, had a prior SARS-CoV-2 infection, or were incarcerated. While the parent study included COVID-negative participants, only COVID-positive participants were included for this analysis.

Viral Variant Exposure

The CDC's national genomic surveillance system collects SARS-CoV-2 specimens for sequencing through the National SARS-CoV-2 Strain Surveillance program, commercial and academic laboratories contracted by the CDC, and state and local public health laboratories. Viral genomic sequences are analyzed and classified [4]. The proportions of variants in a population are estimated nationally, by region, and by jurisdiction [24]. We identified dates when the Delta and Omicron strains became dominant (>50% of new infections attributed to each

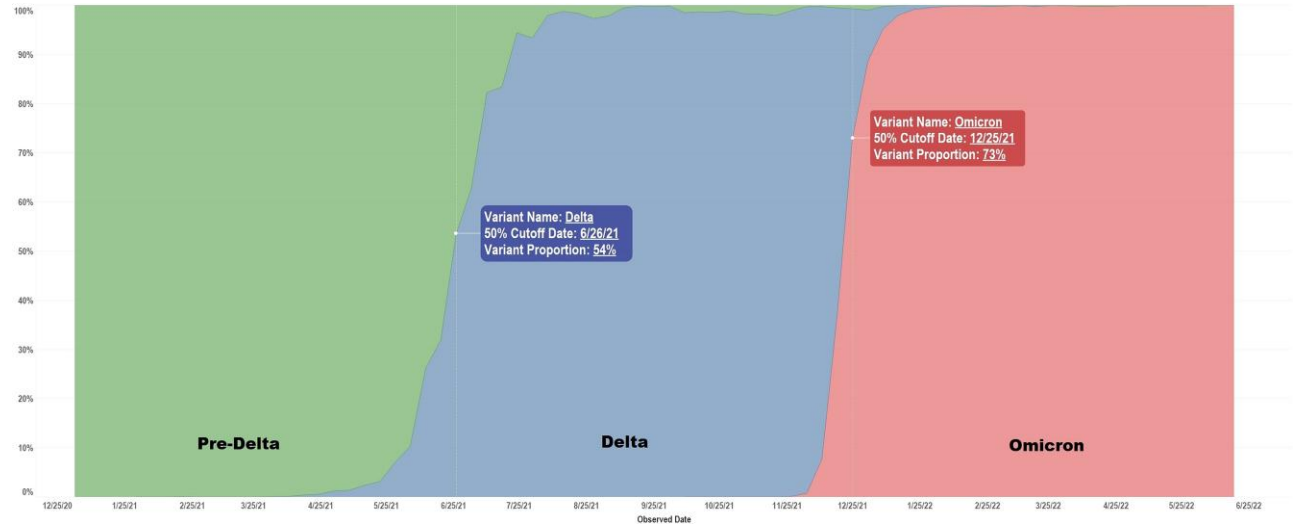

Figure 1. SARS-CoV-2 viral variant proportion over time in the United States (12/25/20–6/25/22). Abbreviation: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

viral variant) in the United States, which allowed us to define 3 periods of VOC dominance [24, 25]. The INSPIRE study began enrollment on 12/20/2020, during the pre-Delta period. Pre-Delta was defined as all participants tested before 6/25/2021. Delta was defined as tested from 6/26/2021 to 12/24/2021. Omicron was defined as tested from 12/25/2021 to 6/25/2022 (Figure 1). Each participant was then assigned to a variant time period based on self-reported date of symptom onset in INSPIRE baseline surveys.

Study Outcomes

The primary outcome was the prevalence of reporting a given COVID-19 symptom. We surveyed study participants after a diagnosis of COVID-19 to assess the presence of physical symptoms based on the CDC Person Under Investigation (PUI) symptoms list. From the PUI symptoms list, 21 individual symptoms were assessed (tired, chills, feeling hot, fever, shakes, headache, runny nose, loss of smell, loss of taste, sore throat, loss of hair, cough, shortness of breath, wheezing, chest pain, palpitations, diarrhea, nausea or vomiting, abdominal pain, aches, and joint pains), classified within 1 of 6 categories: (1) constitutional; (2) head, ears, eyes, nose, and throat (HEENT); (3) pulmonary; (4) gastrointestinal; (5) musculoskeletal; or (6) cardiovascular [19].

Analytic Approach

We described the characteristics of the study participants with COVID overall and by time period, including demographics, socioeconomic status, self-reported preexisting medical conditions, and details of the visit during which they were tested. In addition, we reported COVID-19 vaccination initiation status, defined as a participant with evidence of at least 1 dose of COVID-19 vaccine before the index enrollment SARS-CoV-2 test. Limited vaccination information was obtained from linked EHR data, and follow-up patient survey responses enabled us to classify whether participants received at least 1 dose. We compared sociodemographic and clinical characteristics of groups using chi-square and *t* tests for categorical and continuous variables. We then determined prevalence of individual symptoms at the time of illness onset among COVID-19-positive participants and tested whether the distribution of symptoms differed across variants using independent chi-square tests.

To determine if our results were sensitive to misclassification of variant group, we conducted a sensitivity analysis in which we defined time periods of variant dominance as ≥90% of new infections attributed to the variant, rather than ≥50%. This allowed us to compare the study outcomes when participant exposures were categorized with increased certainty but reduced cohort sizes. These thresholds were defined as: pre-Delta (before 6/4/2021), Delta (7/24/2021 to 12/17/2021), and Omicron (1/8/2022 to 6/25/2022).

We fit 2 multivariable logistic regression models to examine the difference in developing individual symptoms and symptom categories among participants infected during the pre-Delta, Delta, and Omicron periods. Prior studies assessing differences in symptoms between Omicron and Delta accounted for age, sex, comorbidities, and vaccination status [15, 26]. We also adjusted these covariates but in 2 steps. The primary model only accounted for the demographics (age, gender, race, and ethnicity) that were collected at enrollment to maximize the number of participants (n = 3841) in the model. We further fit a secondary model that additionally adjusted for the 9 preexisting comorbidities reported in Table 1 (eg, asthma, chronic obstructive pulmonary disease, diabetes, obesity,

Table 1. Characteristics of the COVID+ Study Participants by Variant Time Period

Variant Time Periods (Classified by Variant Dominance >50%)	Overall (n = 4113)	Pre-Delta (n = 714)	Delta (n = 1553)	Omicron (n = 1846)	*P* Value
Sociodemographics					
Age[a]					<.001
18–34 y	1694 (41.5)	243 (34.1)	671 (43.3)	780 (43.0)	
35–49 y	1323 (32.4)	211 (29.6)	491 (31.7)	621 (34.2)	
50–64 y	748 (18.3)	192 (26.9)	268 (17.3)	288 (15.9)	
65+ y	314 (7.7)	67 (9.4)	121 (7.8)	126 (6.9)	
Gender[a]					.007
Female	2665 (66.6)	452 (64.8)	985 (64.7)	1228 (69.0)	
Male	1283 (32.1)	243 (34.8)	514 (33.8)	526 (29.6)	
Transgender/nonbinary/other	51 (1.3)	3 (0.4)	23 (1.5)	25 (1.4)	
ethnicity[a]					.520
Non-Hispanic	3439 (85.4)	594 (84.6)	1321 (86.2)	1524 (85.0)	
Hispanic	589 (14.6)	108 (15.4)	212 (13.8)	269 (15.0)	
Race[a]					<.001
American Indian/Alaskan Native	25 (0.6)	5 (0.7)	12 (0.8)	8 (0.5)	
Asian/Native Hawaiian/Pacific Islander	513 (12.9)	34 (4.9)	176 (11.6)	303 (17.1)	
Black	366 (9.2)	183 (26.5)	99 (6.5)	84 (4.7)	
Other	333 (8.3)	49 (7.1)	129 (8.5)	155 (8.7)	
White	2755 (69.0)	421 (60.8)	1107 (72.7)	1227 (69.1)	
Education[a]					<.001
Less than high school	58 (1.5)	26 (3.8)	19 (1.3)	13 (0.7)	
High school graduate	310 (7.8)	143 (20.7)	77 (5.1)	90 (5.1)	
Some college	560 (14.1)	122 (17.7)	240 (15.9)	198 (11.2)	
2-y degree	285 (7.2)	66 (9.6)	115 (7.6)	104 (5.9)	
4-y degree	1331 (33.5)	176 (25.5)	555 (36.8)	600 (33.9)	
>4-y degree(s)	1429 (36.0)	158 (22.9)	504 (33.4)	767 (43.3)	
Marital status[a]					<.001
Married/partner	2246 (55.2)	361 (52.1)	896 (58.2)	989 (53.8)	
Divorced/widowed/separated	409 (10.1)	97 (14.0)	157 (10.2)	155 (8.4)	
Never married	1415 (34.8)	235 (33.9)	487 (31.6)	693 (37.7)	
Family income[a]					<.001
<10 000	231 (5.7)	66 (9.6)	80 (5.2)	85 (4.6)	
10 000–34 999	433 (10.6)	125 (18.1)	140 (9.1)	168 (9.2)	
35 000–49 999	379 (9.3)	85 (12.3)	149 (9.7)	145 (7.9)	
50 000–74 999	545 (13.4)	111 (16.1)	207 (13.4)	227 (12.4)	
75 000+	2225 (54.7)	290 (42.0)	859 (55.8)	1076 (58.6)	
Prefer not to answer	255 (6.3)	14 (2.0)	105 (6.8)	136 (7.4)	
Health insurance[a]					<.001
Private	3003 (73.0)	427 (59.8)	1130 (72.8)	1446 (78.3)	
Public	773 (18.8)	201 (28.2)	295 (19.0)	277 (15.0)	
Private and pubic	134 (3.3)	26 (3.6)	59 (3.8)	49 (2.7)	
Self-insured	203 (4.9)	60 (8.4)	69 (4.4)	74 (4.0)	
Employment[a]					<.001
Employed, essential	1704 (41.9)	289 (41.6)	618 (40.2)	797 (43.4)	
Employed, nonessential	1661 (40.8)	247 (35.5)	687 (44.7)	727 (39.6)	
Not employed	704 (17.3)	159 (22.9)	233 (15.2)	312 (17.0)	
Clinical characteristics[a]					
Tobacco use					.007
Daily	240 (5.9)	38 (5.5)	105 (6.8)	97 (5.3)	
Weekly	75 (1.8)	22 (3.2)	31 (2.0)	22 (1.2)	
Monthly	61 (1.5)	13 (1.9)	19 (1.2)	29 (1.6)	
Less than monthly	214 (5.3)	25 (3.6)	83 (5.4)	106 (5.8)	
Not at all	3480 (85.5)	598 (85.9)	1300 (84.5)	1582 (86.2)	

Table 1. Continued

Variant Time Periods (Classified by Variant Dominance >50%)	Overall (n = 4113)	Pre-Delta (n = 714)	Delta (n = 1553)	Omicron (n = 1846)	*P* Value
COVID testing site[a]					<.001
At home	508 (12.4)	4 (0.6)	69 (4.5)	435 (23.6)	
Clinic including urgent care	551 (13.4)	102 (14.4)	258 (16.7)	191 (10.4)	
Emergency department	185 (4.5)	92 (13.0)	60 (3.9)	33 (1.8)	
Hospital	354 (8.6)	149 (21.1)	95 (6.1)	110 (6.0)	
Other	272 (6.6)	39 (5.5)	91 (5.9)	142 (7.7)	
Tent/drive-up testing site	2233 (54.4)	321 (45.4)	977 (63.0)	935 (50.7)	
Preexisting conditions[a,b]					.000
Asthma	287 (12.2)	55 (12.8)	146 (12.4)	86 (11.7)	
Hypertension	327 (13.9)	79 (18.3)	166 (14.1)	82 (11.1)	
Diabetes	119 (5.1)	28 (6.5)	52 (4.4)	39 (5.3)	
Obesity	640 (27.3)	134 (31.1)	316 (26.9)	190 (25.8)	
Emphysema/COPD	20 (0.9)	10 (2.3)	7 (0.6)	3 (0.4)	
Heart conditions	57 (2.4)	21 (4.9)	24 (2.0)	12 (1.6)	
Smoking	102 (4.4)	26 (6.0)	53 (4.5)	23 (3.1)	
Kidney disease	31 (1.3)	6 (1.4)	16 (1.4)	9 (1.2)	
Liver disease	18 (0.8)	10 (2.3)	5 (0.4)	3 (0.4)	
Other	352 (15.0)	64 (14.9)	180 (15.3)	108 (14.7)	
None	429 (18.3)	57 (13.2)	228 (19.4)	144 (19.5)	
Don't know	521 (22.2)	96 (22.3)	257 (21.8)	168 (22.8)	
Prefer not to answer	126 (5.4)	25 (5.8)	50 (4.3)	51 (6.9)	
Hospitalized for COVID[b]					<.001
Not hospitalized	2214 (94.4)	374 (86.8)	1122 (95.3)	718 (97.6)	
Hospitalized	131 (5.6)	57 (13.2)	56 (4.8)	18 (2.5)	
Vaccination initiation[c]					<.001
Unvaccinated before index test	740 (26.8)	432 (80.7)	308 (26.1)	9 (0.9)	
Vaccinated before index test	2026 (73.3)	101 (19.3)	874 (73.9)	1051 (99.2)	

Abbreviations: COPD, chronic obstructive pulmonary disease; COVID, coronavirus disease; EHR, electronic health record.

[a]The missing numbers differ across the characteristics and range from 0 to 140 (3.4%). We did not observe systematic patterns in missingness and therefore assumed missingness at random. The % and *P* values were all calculated after excluding missingness.

[b]Question asked on 3-month follow-up survey; 1685 participants did not complete the 3-month follow-up survey.

[c]Vaccination status questions based on all available EHR and survey data; 1347 participants were missing vaccine information.

hypertension, smoking) and vaccination initiation status collected during follow-up surveys. The secondary model included approximately half of the participants (n = 1847) from the primary model. Data analyses were conducted using SAS 9.4. *P* values <.05 were considered significant.

RESULTS

Study Enrollment

At the time of this analysis, 8298 individuals were screened for participation; 2816 were excluded due to incomplete enrollment, ineligibility, or withdrawal from the study, leaving 5482 enrolled in the study. Of these, 4113 tested positive for COVID-19 on their index test, completed baseline surveys, and were included in the analysis (Figure 2).

Participant Characteristics

Seven hundred fourteen (17.4%) participants were enrolled during pre-Delta, 1553 (37.8%) during Delta, and 1846 (44.9%) during Omicron. The sociodemographic and clinical characteristics of the participants varied by variant period (Table 1). Participants enrolled during Omicron were noted to have significantly different demographic, socioeconomic, and clinical characteristics compared with participants enrolled during pre-Delta or Delta. Omicron participants were less likely to be ≥50 years of age, Black, or have public insurance compared with pre-Delta and Delta participants. Omicron participants were less likely to be tested in the emergency department or hospital, have preexisting comorbidities, or require hospitalization compared with pre-Delta and Delta participants. During pre-Delta, 57/714 (13.2%) were hospitalized, compared with 56/1553 (4.8%) during Delta and 18/1846 (2.5%) during Omicron ($P < .001$). In addition, 99.2% of Omicron participants initiated vaccination before their index diagnostic test for SARS-CoV-2, as compared with 19.3% of pre-Delta and 73.9% of Delta participants.

Symptom Prevalence

The profile of acute infection symptoms differed by variant period. Significant differences in unadjusted prevalence were

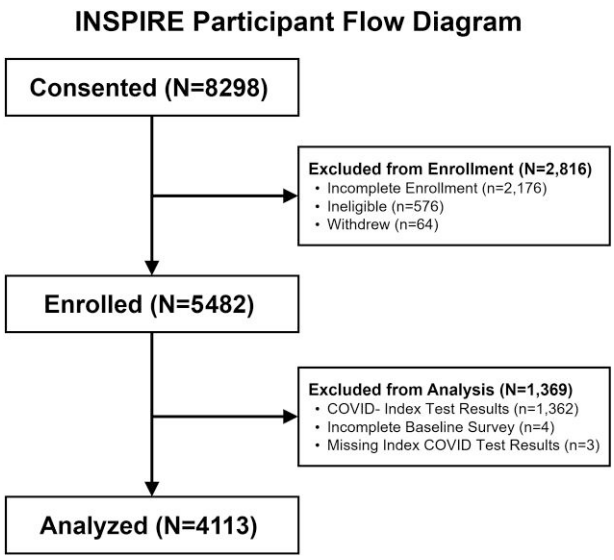

Figure 2. INSPIRE participant flow diagram. Abbreviation: INSPIRE, Innovative Support for Patients with SARS-CoV-2 Infections Registry.

noted for 19 of 21 individual symptoms (Table 2). Among the pre-Delta, Delta, and Omicron periods, we observed an increasing prevalence of sore throat (40.9%, 54.6%, 70.6%; $P < .001$), cough (50.9%, 63.3%, 66.7%; $P < .001$), and runny nose (48.9%, 71.3%, 72.9%; $P < .001$). We observed reductions in chest pain (31.1%, 24.2%, 20.9%; $P < .001$), diarrhea (30.7%, 22.9%, 18.2%; $P < .001$), and shortness of breath (42.7%, 29.5%, 27.5%; $P < .001$) across the 3 periods. Loss of taste (47.1%, 61.8%, 19.2%; $P < .001$) and loss of smell (47.5%, 55.6%, 20.0%; $P < .001$) increased during Delta and then decreased during Omicron.

In our primary model, after adjustment for age, sex, race, and ethnicity, Omicron was associated with significantly higher odds of sore throat (odds ratio [OR], 2.76; 95% CI, 2.26–3.35; vs pre-Delta; and OR, 1.96; 95% CI, 1.69–2.28; vs Delta) and cough (OR, 1.70; 95% CI, 1.40–2.07; vs pre-Delta; and OR, 1.17; 95% CI, 1.01–1.36; vs Delta). Omicron had significantly lower odds in 16 of 21 individual symptoms (including chills, fever, shakes, loss of smell, loss of taste, loss of hair, shortness of breath, chest pain, palpitations, diarrhea, nausea and vomiting, abdominal pain, and joint pains) compared with pre-Delta and lower odds in 13 of 21 individual symptoms compared with Delta (Figure 3; Supplementary Appendix 2). Of note, Omicron was associated with lower odds of loss of smell (OR, 0.22; 95% CI, 0.18–0.27; vs pre-Delta; and OR, 0.13; 95% CI, 0.11–0.16; vs Delta) and loss of taste (OR, 0.23; 95% CI, 0.19–0.28; vs pre-Delta; and OR, 0.19; 95% CI, 0.16–0.22; vs Delta).

In our first sensitivity analysis defining VOC dominance as a viral variant exceeding 90% of the circulating virus, unadjusted symptom prevalence did not differ by >1% from the primary analysis (Supplementary Appendix 1), and odds ratios were similar (Supplementary Appendix 2).

In our secondary model (Supplementary Appendix 2), we added comorbidities and vaccination status to the model, in addition to age, sex, race, and ethnicity. The association between Omicron and sore throat remained significant (OR, 1.61; 95% CI, 1.13–2.30; vs pre-Delta; and OR, 1.67; 95% CI, 1.30–2.14; vs Delta). We found that the association between Omicron with some symptoms (including constitutional, cardiovascular, cardiac, and musculoskeletal symptoms) was moderately changed after adding these additional covariates. However, the reduced odds of loss of smell and taste did not change substantially.

DISCUSSION

In a multi-institutional cohort of adults who tested positive for SARS-CoV-2, participants infected during Omicron were more likely to report symptoms of common respiratory viruses, such as sore throat, and less likely to report "pathognomonic" loss of smell and taste. Many of these findings (lower odds of fever, loss of smell and taste, diarrhea, and increased odds of sore throat) persisted after controlling for participant age, sex, race, and ethnicity.

Our study builds upon findings of other studies reporting that Omicron was associated with a lower prevalence of multiple acute symptoms except for sore throat. A UK study reported similar changes in acute symptoms, including increased odds of sore throat and decreased odds of loss of smell during Omicron compared with Delta after adjusting for age, sex, comorbidities, and vaccination status [15]. Another study reported lower rates of olfactory dysfunction in Omicron after adjusting for age, sex, time since symptom onset, vaccination status, and comorbidities [27]. The results from both our primary and secondary models including age, race, ethnicity, gender, comorbidities, and vaccination status confirm that Omicron-infected patients in the United States had greater odds of reporting sore throat compared with Delta. We also confirm that Omicron had lower odds of fever, loss of smell and taste, and diarrhea compared with Delta. Our findings add to this evidence by including participants from the pre-Delta period and providing data from the United States. As we concluded enrollment in June of 2022, we were also able to include a broader array of Omicron subvariants compared with prior studies.

Potential explanations for the observed change in clinical symptoms over time include differences in characteristics of the SARS-CoV-2 variants and the interaction between viral and host factors, including age, comorbidities, vaccine-derived and natural immunity, and improvements in medical treatments. The Omicron virus contains multiple mutations in its spike protein, resulting in increased transmissibility and ability to evade vaccine-derived neutralizing antibodies [28, 29]. Interestingly, in vitro studies have shown that while Omicron

Table 2. Proportion of COVID+ Study Participants With Acute Symptoms by Variant of Concern Time Period

	Overall (n = 4077)		Pre-Delta (n = 701)		Delta (n = 1541)		Omicron (n = 1835)		
Symptom Category	No.	%	No.	%	No.	%	No.	%	*P* Value
Any constitutional	3580	87.8	601	85.7	1371	89.0	1608	87.6	.090
Tired	3284	80.6	538	76.8	1280	83.1	1466	79.9	.001
Chills	2070	50.8	384	54.8	807	52.4	879	47.9	.002
Feeling hot	1924	47.2	286	40.8	791	51.3	847	46.2	<.001
Fever	1266	31.1	244	34.8	528	34.3	494	26.9	<.001
Shakes	634	15.6	138	19.7	247	16.0	249	13.6	<.001
Any HEENT	3799	93.2	602	85.9	1467	95.2	1730	94.3	<.001
Headache	2671	65.5	442	63.1	1053	68.3	1176	64.1	.011
Runny nose	2778	68.1	343	48.9	1098	71.3	1337	72.9	<.001
Loss of smell	1636	40.1	330	47.1	953	61.8	353	19.2	<.001
Loss of taste	1557	38.2	333	47.5	857	55.6	367	20.0	<.001
Sore throat	2424	59.5	287	40.9	841	54.6	1296	70.6	<.001
Loss of hair	146	3.6	34	4.9	62	4.0	50	2.7	.018
Any pulmonary	2906	71.3	465	66.3	1092	70.9	1349	73.5	.002
Cough	2557	62.7	357	50.9	976	63.3	1224	66.7	<.001
Shortness of breath	1259	30.9	299	42.7	455	29.5	505	27.5	<.001
Wheezing	460	11.3	89	12.7	178	11.6	193	10.5	.275
Any cardiovascular	1116	27.4	237	33.8	422	27.4	457	24.9	<.001
Chest pains	975	23.9	218	31.1	373	24.2	384	20.9	<.001
Palpitation	336	8.2	69	9.8	127	8.2	140	7.6	.193
Any gastrointestinal	1417	34.8	315	44.9	549	35.6	553	30.1	<.001
Diarrhea	902	22.1	215	30.7	353	22.9	334	18.2	<.001
Nausea or vomiting	738	18.1	166	23.7	271	17.6	301	16.4	<.001
Abdominal pain	467	11.5	103	14.7	184	11.9	180	9.8	.002
Any musculoskeletal	2478	60.8	441	62.9	960	62.3	1077	58.7	.046
Aches	2374	58.2	420	59.9	919	59.6	1035	56.4	.101
Joint pains	1221	30.0	245	35.0	483	31.3	493	26.9	<.001
3+ symptoms (not including other)	3705	90.8	607	86.5	1455	94.4	1643	89.5	<.001
Other symptoms	511	12.5	70	10.0	229	14.9	212	11.6	.001
No symptoms	53	1.3	29	4.1	12	0.8	12	0.7	<.001

Table 2 excludes participants (n = 36) with missing responses for symptoms prevalent at baseline.

Abbreviations: COVID, coronavirus disease; HEENT, head, ears, eyes, nose, and throat.

replicates in a similar fashion to Delta in nasal epithelial cells [29], Omicron replication is reduced in lung cells and gut cells, which may explain decreased symptoms of shortness of breath and gastrointestinal symptoms [30]. It is unclear what explains the differences in loss of smell and taste that we observed. In addition, the population captured in the study changed significantly over the different variant time periods: Omicron participants were less likely to be older, Black, or unvaccinated, to have preexisting comorbidities, or to require hospitalization compared with pre-Delta and Delta participants. Our data collection mechanism did not change, so this change may simply reflect changes in epidemiology over time. However, we do not know the extent to which epidemiological changes drove the changes in enrollment, or if there was some other mechanism that might bias enrollment. We attempted to estimate the effect of viral variant by adjusting for race, ethnicity, age, sex, comorbidities, and vaccination status and still found significant differences in the odds of several symptoms. Conversely, we would note that understanding the racial and ethnic differences in variants is essential to understanding if there is, and to what extent there is, differential impact of long COVID by race/ethnicity.

On a broader note, conventional theories of evolution might hold that successful pandemic pathogens must evolve to cause milder illness, lest they exhaust susceptible hosts in the population [31]. Prior studies comparing patients infected with Omicron with those infected with Delta have found lower rates of mortality and hospitalization [10, 11, 13]. We found lower unadjusted rates of hospitalization in our study. However, despite what appears to be lower disease severity, investigators have reported higher excess mortality during Omicron due to increased transmissibility and huge increases in absolute numbers of cases [14]. We observed that COVID-19 symptomatology currently appears to be evolving from an illness originally characterized by fatigue, fever, and pulmonary, gastrointestinal, and neurologic symptoms to one with fewer symptoms (with the exception of sore throat). Clinicians should adjust

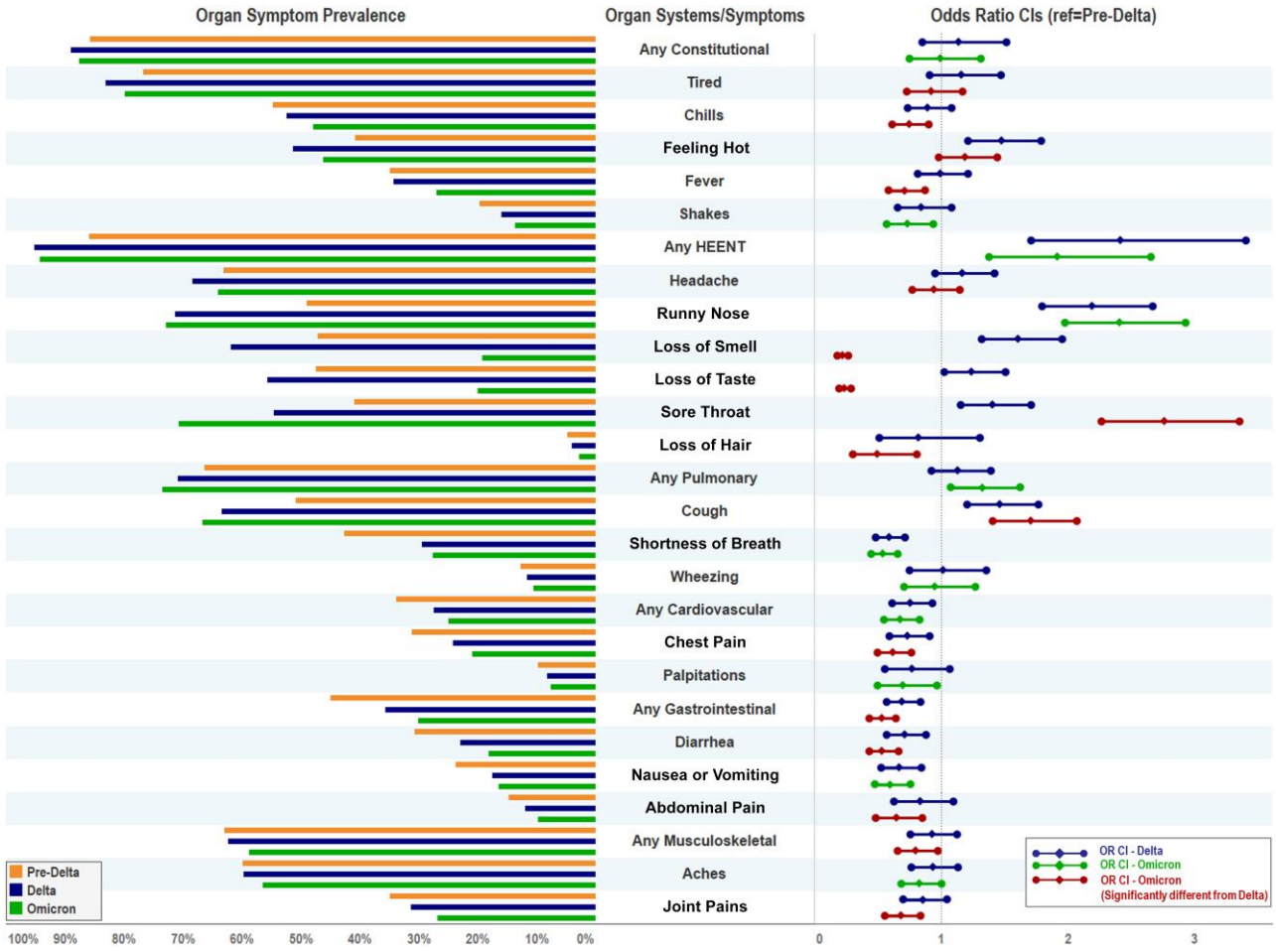

Figure 3. Bar chart of acute symptom prevalence and Forest plot of odds ratios for each acute symptom by variant time period (variant was >50% of circulating virus).

their estimation of the pretest probability of COVID-19 to include those with even mild upper respiratory infection symptoms, such as sore throat, runny nose, and cough. Providers should recognize that loss of smell and loss of taste, once considered pathognomonic for COVID-19 infection, are far less prevalent. Patients should be aware that the symptom profile of COVID-19 is changing as the virus evolves and seek testing for mild symptoms. Also, as post-COVID recovery may be marked by several persistent conditions, such as impaired concentration, headache, sensory disturbances, and depression, understanding how these differ at disease onset by variant is important. For example, researchers studying long COVID should recognize that Omicron is associated with significantly lower odds of initial loss of smell and taste at the time of acute illness, and therefore loss of smell and taste maybe a less common long COVID symptom in this variant population [32].

We note some study limitations. As an ecological study, we did not directly measure viral genome sequence. Prior studies have used circulating virus benchmarks of >50% or >75% [15, 33]. We conducted a sensitivity analysis in which we identified time periods when pre-Delta, Delta, and Omicron consisted of >90% of circulating viruses in the United States and found that the differences in symptom prevalence varied little compared with results from our analysis using >50% of circulating virus, which reflects the rapid transitions between dominant strains and validates our cut-points for future studies of this pandemic.

A second limitation reflects the challenges of analyzing real-world pandemic data. We attempted to control for the fact that more elderly and Black patients were infected early in the pandemic with adjusted analyses. In addition, we attempted to account for the impact of vaccination by including vaccination initiation status in a secondary model; however, vaccination data were not available for all participants, and we were unable to include whether the vaccination series was completed or how long before the illness vaccination occurred. In addition, our data demonstrated evidence of collinearity between vaccination status and the variant time period, reflecting the real-world changes in the epidemiology of the COVID-19 pandemic and vaccination efforts. Similarly, we were unable to account for

the use of COVID-19 treatments, including antiviral medications and monoclonal antibodies. These limitations are likely to be important, as is suggested by recent data from Hong Kong describing increased mortality during Omicron in unvaccinated seniors [34].

Other limitations include our inability to include newer variants such as BA.5 (which became the dominant US subvariant in July 2022), which may have a different symptom profile. Our study also is vulnerable to potential selection bias, as we required that participants had access to an internet-capable device. Also, we required that participants submit survey responses within 42 days of enrollment, and the time interval between enrollment and survey responses was 19.4 days. This may have allowed for some recall bias, but the direction of this bias across viral variants is unclear.

The strengths of this study include its use of a prospective study design and robust data collection that directly acquired patient-reported symptoms within weeks of acute confirmed SARS-CoV-2 infection. By not relying on EHR extraction, we presented "first-hand" data and included patients who may not have sought medical care (eg, there would not be any information about these individuals' symptoms within EHRs, and thus they would not be included in a study that relied exclusively on EHR extraction), which provides us with a more generalizable cohort of individuals. Second, this study was conducted at 8 academic centers across the United States. We intentionally selected sites for geographic and sociodemographic diversity, and sites were not limited to enrolling individuals from within their health system. Thus, we broadly recruited patients throughout the United States with no limitations on state of residence. It is likely that these results reflect the COVID-19-related experiences of similar patients throughout the United States.

CONCLUSIONS

The clinical presentation of acute infection with SARS-CoV-2 differed considerably during the Omicron variant period compared with the pre-Delta and Delta variant time periods. Compared with Delta, those infected with Omicron were significantly more likely to experience sore throat and less likely to experience fever, loss of smell and taste, and diarrhea, even when accounting for vaccination initiation status. As SARS-CoV-2 virus continues to evolve and new VOCs emerge, continued tracking and monitoring of acute symptoms at the onset of clinical illness are invaluable to our epidemiologic understanding of this pandemic and to inform public health screening and clinical diagnostic programs.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Acknowledgments

INSPIRE Investigators. **Rush University, Administrative Core & Enrolling Site:** Study-wide Co-Principal Investigators: Robert A. Weinstein, MD, Principal Investigator; Michael Gottlieb, MD, Principal Investigator. Core research team: Michelle Santangelo, MS, Administrative Core Program Manager; Katherine Koo, MS-HSM, Publications Committee Program Manager; Antonia Derden, BA, Administrative Assistant. Site Investigators: Michael Gottlieb, MD, Site Principal Investigator. Site research team: Kristyn Gatling, MS, Research Coordinator; Diego Guzman, Research Assistant; Geoffrey Yang, BS, Research Assistant; Marshall Kaadan, BS, Research Assistant; Minna Hassaballa, BS, Research Assistant; Ryan Jerger, Research Assistant; Zohaib Ahmed, BS, Research Assistant; Michael Choi, BS, Research Assistant. **Yale University, Analytic Core & Enrolling Site:** Core Investigators: Arjun K. Venkatesh, MD, MBA, MHS, Principal Investigator; Erica Spatz MD, MHS, Principal Investigator. Core research team: Zhenqiu Lin, PhD, Core Statistician; Shu-Xia Li, PhD, Core Statistician; Huihui Yu, PhD, Core Statistician; Mengni Liu, MS, Core Statistician. Site Investigators: Arjun K. Venkatesh, MD, MBA, MHS, Site Principal Investigator; Erica Spatz MD, MPH, Site Principal Investigator; Andrew Ulrich, MD, Co-Investigator. Site research team: Jeremiah Kinsman, MPH, NREMT, Research Coordinator; Jocelyn Dorney, MPH, Research Coordinator; Senyte Pierce, Research Assistant; Xavier Puente, Research Assistant. **University of Washington, Clinical Core & Enrolling Site:** Core Investigators: Graham Nichol, MD, Principal Investigator; Kari Stephens PhD, MS, Principal Investigator. Core research team: Jill Anderson, BSN, RN, Clinical Core Program Manager; Dana Morse, RN, BSN, Research Coordinator; Karen Adams, BA, Regulatory Specialist; Zenoura Maat, Research Assistant; Tracy Stober, BA, MA, Patient Representative. Site Investigators: Kelli N. O'Laughlin, MD, MPH, Site Principal Investigator; Nikki Gentile, MD, PhD, Co-Investigator. Site research team: Rachel E. Geyer, MPH, Research Coordinator; Michael Willis, AS, BSHS, Research Coordinator; Luis Ruiz, BA, Research Assistant; Kerry Malone, BA, Research Assistant; Jasmine Park, Research Assistant. **Thomas Jefferson University, Enrolling Site:** Site Investigators: Kristin Rising, MD, MS, Site Principal Investigator; Efrat Kean, MD, Co-Investigator. Site research team: Morgan Kelly, BS, Research Coordinator; Kevin Schaeffer, Research Coordinator; Paavali Hannikainen, BS, Research Assistant; Lindsey Shughart, BS, Research Assistant; Hailey Shughart, BA, CCRP, Research Assistant; Nicole Renzi, RN, Nurse Coordinator; Grace Amadio, Research Assistant; Dylan Grau, Research Coordinator; Phillip Watts, BA, MM, CCRP, Research Coordinator; David Cheng, BS, Research Coordinator; Jessica Miao, BA, Research Assistant; Carly Shutty, BSN, Research Coordinator; Alex Charlton, Research Coordinator. **University of Texas Health Science Center at Houston, Enrolling Site:** Site Investigators: Mandy Hill, DrPH, MPH, Site Principal Investigator; Ryan Huebinger Site, MD, Site Principal Investigator; Summer Chavez, DO, MPH, MPM, Co-Investigator. Site research team: Arun Kane, BA, Research Assistant; Peter Nikonowicz, Research Assistant. University of Texas Southwestern Medical Center, Enrolling Site. Site Investigators: Ahamed H. Idris, MD, Site Principal Investigator; Samuel McDonald, MD, Co-Investigator. Site research team: David Gallegos, Research Coordinator; Riley Martin, Research Assistant. **University of California, Los Angeles, Enrolling Site:** Site Investigators: Joann Elmore, MD, MPH, Site Principal Investigator, Lauren Wisk, PhD, Co-Investigator. Site research team: Michelle L'Hommedieu, PhD, Site Program Director; Chris Chandler, BA, Research Assistant; Megan Eguchi, MPH, Data Analyst; Kate Diaz Roldan, MPH, Research Assistant; Nicole Villegas, BS, Research Assistant; Raul Moreno, BA, Administrative Analyst. **University of California, San Francisco, Enrolling Site:** Site Investigators: Robert M. Rodriguez, MD, Site Principal Investigator; Ralph C. Wang, MD, MAS, Site Principal Investigator; Juan Carlos C. Montoy, MD, PhD, Site Principal Investigator. Site research team: Robin Kemball, MPH, Program Manager; Virginia Chan, BS, Research

Coordinator; Cecilia Lara Chavez, Research Coordinator; Angela Wong, BA, Research Coordinator; Mireya Arreguin, Research Coordinator. **California Department of Public Health:** We would like to thank California Department of Public Health for their assistance with participant recruitment for this study. **CTSI COVID Clinical Research Steering Committee and the CTSI Office of Clinical Research Patient Navigation Team and Bioinformatics Program:** We would like to thank the CTSI COVID Clinical Research Steering Committee and the CTSI Office of Clinical Research Patient Navigation Team and Bioinformatics Program for assistance with study recruitment. **Centers for Disease Control and Prevention**

Investigators: Ian D. Plumb, MBBS, MSc; Aron J. Hall, DVM, MSPH; Sharon Saydah, PhD; Melissa Briggs-Hagen, MD, MPH.

Financial support. The Innovative Support for Patients with SARS-COV-2 Infections Registry (INSPIRE) is funded by the National Center of Immunization and Respiratory Diseases, Centers for Disease Control and Prevention (NCIRD; contract number: 75D30120C08008; PI, Robert A. Weinstein, MD). Partners from the CDC (Ian D. Plumb, MBBS, MSc, Sharon Saydah, PhD, MHS) assisted with study design and the preparation of this manuscript.

Potential conflicts of interest. Dr. Elmore reports serving as Editor in Chief of Adult Primary Care topics for UpToDate. Dr. Venkatesh reports funding for COVID-19-related studies from the Society of Academic Emergency Medicine Foundation Emerging Infectious Disease and Preparedness Grant, the Agency for Healthcare Research and Quality (R01 HS 28340-01) the Food and Drug Administration (ID: 75F40120C00174), and the Emergency Medicine Health Policy Institute/Emergency Medicine Foundation. Dr. Wang reports funding from CDC for research on N95 respirators. Dr. Gottlieb reports grant funding from the Rush Center for Emerging Infectious Diseases Research Grant, Emergency Medicine Foundation/Council of Residency Directors in Emergency Medicine Education Research Grant, Emergency Medicine: Reviews and Perspectives Medical Education Research Grant, University of Ottawa Department of Medicine Education Grant; and Society of Directors of Research in Medical Education Grant. Dr. Nichol reports the following: Vapotherm Inc, Exeter, NH- Research funding; ZOLL Medical, Chelmsford, MA- Research funding; Abiomed Inc., Danvers, MA- Consultant; CellPhire Inc., Rockville, MD- Consultant; CPR Therapeutics, Putney, VT- Consultant; ZOLL Circulation, San Jose, CA-Consultant; Patent- Method for non-imaging ultrasound to measure blood flow during CPR; Non-provisional patent- Method for modifying cell injury associated with reduced blood flow; Heartbeam Inc., Santa Clara, CA-Consultant; Invero Health, LLC., Montvale, NJ- Consultant; Orixha Inc., Saint Cyr Au Mont d'Or, France- Consultant; Kestra Medical Technologies, Kirkland, WA- Consultant; Medic One Foundation, Seattle, WA- Salary Support via Univ. Washington (UW). Dr. Elmore reports serving as Editor in Chief of Adult Primary Care topics for UpToDate. Dr. Venkatesh reports funding for COVID-19-related studies from the Society of Academic Emergency Medicine Foundation Emerging Infectious Disease and Preparedness Grant, the Agency for Healthcare Research and Quality (R01 HS 28340-01), the Food and Drug Administration (ID: 75F40120C00174), and the Emergency Medicine Health Policy Institute/Emergency Medicine Foundation. Dr. Wang reports funding from CDC for research on N95 respirators. All other authors report no potential conflicts.

Disclaimer. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention (CDC).

References

1. Galloway SE, Paul P, MacCannell DR, et al. Emergence of SARS-CoV-2 B.1.1.7 lineage—United States, December 29, 2020-January 12, 2021. MMWR Morb Mortal Wkly Rep **2021;** 70:95–9.
2. National Center for Immunization and Respiratory Diseases (NCIRD) DoVD. Science brief: emerging SARS-CoV-2 variants. Centers for Disease Control and Prevention (US). CDC COVID-19 science briefs. Published **2020**. Available at: https://www.ncbi.nlm.nih.gov/books/NBK570441/. Accessed April 30, 2022.
3. Firestone MJ, Lorentz AJ, Wang X, et al. First identified cases of SARS-CoV-2 variant B.1.1.7 in Minnesota—December 2020-January 2021. MMWR Morb Mortal Wkly Rep **2021;** 70:278–9.
4. Center for Disease Control and Prevention. SARS-CoV-2 variant classifications and definitions. COVID-19. Published **2022**. Available at: https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-classifications.html#concern. Accessed August 4, 2022.
5. Lambrou AS, Shirk P, Steele MK, et al. Genomic surveillance for SARS-CoV-2 variants: predominance of the Delta (B.1.617.2) and Omicron (B.1.1.529) variants—United States, June 2021-January 2022. MMWR Morb Mortal Wkly Rep **2022;** 71:206–11.
6. Paul P, France AM, Aoki Y, et al. Genomic surveillance for SARS-CoV-2 variants circulating in the United States, December 2020-May 2021. MMWR Morb Mortal Wkly Rep **2021;** 70:846–50.
7. World Health Organization. Tracking SARS-CoV-2 variants. Published **2022**. Available at: https://www.who.int/activities/tracking-SARS-CoV-2-variants. Accessed May 19, 2022.
8. Hachmann NP, Miller J, Collier AY, et al. Neutralization escape by SARS-CoV-2 Omicron subvariants BA.2.12.1, BA.4, and BA.5. N Engl J Med **2022;** 387:86–8.
9. Lewnard JA, Hong VX, Patel MM, Kahn R, Lipsitch M, Tartof SY. Clinical outcomes associated with SARS-CoV-2 Omicron (B.1.1.529) variant and BA.1/BA.1.1 or BA.2 subvariant infection in Southern California. Nat Med **2022;** 28:1933–43.
10. Iuliano AD, Brunkard JM, Boehmer TK, et al. Trends in disease severity and health care utilization during the early Omicron variant period compared with previous SARS-CoV-2 high transmission periods—United States, December 2020-January 2022. MMWR Morb Mortal Wkly Rep **2022;** 71:146–52.
11. Ulloa AC, Buchan SA, Daneman N, Brown KA. Estimates of SARS-CoV-2 Omicron variant severity in Ontario, Canada. JAMA **2022;** 327:1286–8.
12. Wolter N, Jassat W, Walaza S, et al. Early assessment of the clinical severity of the SARS-CoV-2 Omicron variant in South Africa: a data linkage study. Lancet **2022;** 399:437–46.
13. Maslo C, Friedland R, Toubkin M, Laubscher A, Akaloo T, Kama B. Characteristics and outcomes of hospitalized patients in South Africa during the COVID-19 Omicron wave compared with previous waves. JAMA **2022;** 327:583–4.
14. Faust JS, Du C, Liang C, et al. Excess mortality in Massachusetts during the Delta and Omicron waves of COVID-19. JAMA **2022;** 328:74–6.
15. Menni C, Valdes AM, Polidori L, et al. Symptom prevalence, duration, and risk of hospital admission in individuals infected with SARS-CoV-2 during periods of Omicron and Delta variant dominance: a prospective observational study from the ZOE COVID study. Lancet **2022;** 399:1618–24.
16. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. JAMA **2020;** 323:1061–9.
17. Docherty AB, Harrison EM, Green CA, et al. Features of 20 133 UK patients in hospital with COVID-19 using the ISARIC WHO clinical characterisation protocol: prospective observational cohort study. BMJ **2020;** 369:m1985.
18. Grant MC, Geoghegan L, Arbyn M, et al. The prevalence of symptoms in 24,410 adults infected by the novel coronavirus (SARS-CoV-2; COVID-19): a systematic review and meta-analysis of 148 studies from 9 countries. PLoS One **2020;** 15:e0234765.
19. Center for Disease Control and Prevention. Symptoms of COVID-19. Published **2022**. Available at: https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html. Accessed August 4, 2022.
20. Burke RM, Killerby ME, Newton S, et al. Symptom profiles of a convenience sample of patients with COVID-19—United States, January-April 2020. MMWR Morb Mortal Wkly Rep **2020;** 69:904–8.
21. Center for Disease Control and Prevention. Human infection with 2019 novel coronavirus case report form. Available at: https://www.cdc.gov/coronavirus/2019-ncov/downloads/pui-form.pdf. Accessed September 2, 2022.
22. O'Laughlin KN, Thompson M, Hota B, et al. Study protocol for the innovative support for patients with SARS-COV-2 infections registry (INSPIRE): a longitudinal study of the medium and long-term sequelae of SARS-CoV-2 infection. PLoS One **2022;** 17:e0264260.
23. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. BMJ **2007;** 335:806–8.
24. Center for Disease Control and Prevention. SARS-CoV-2 variant proportions. Published **2022**. Available at: https://data.cdc.gov/Laboratory-Surveillance/SARS-CoV-2-Variant-Proportions/jr58-6ysp/data. Accessed August 4, 2022.
25. Taylor CA, Patel K, Pham H, et al. Severity of disease among adults hospitalized with laboratory-confirmed COVID-19 before and during the period of

SARS-CoV-2 B.1.617.2 (Delta) predominance—COVID-NET, 14 states, January-August 2021. MMWR Morb Mortal Wkly Rep **2021;** 70:1513–9.
26. Whitaker M, Elliott J, Bodinier B, et al. Variant-specific symptoms of COVID-19 among 1,542,510 people in England. medRxiv 22275368 [Preprint]. May 23, **2022**. Available at: https://doi.org/10.1101/2022.05.21.22275368. Accessed August 4, 2022.
27. Cardoso CC, Rossi ÁD, Galliez RM, Faffe DS, Tanuri A, Castiñeiras TMPP. Olfactory dysfunction in patients with mild COVID-19 during Gamma, Delta, and Omicron waves in Rio de Janeiro, Brazil. JAMA **2022;** 328:582–3.
28. Cele S, Jackson L, Khoury DS, et al. Omicron extensively but incompletely escapes Pfizer BNT162b2 neutralization. Nature **2022;** 602:654–6.
29. Meng B, Abdullahi A, Ferreira IATM, et al. Altered TMPRSS2 usage by SARS-CoV-2 omicron impacts infectivity and fusogenicity. Nature **2022;** 603:706–14.
30. Hui KPY, Ho JCW, Cheung MC, et al. SARS-CoV-2 Omicron variant replication in human bronchus and lung ex vivo. Nature **2022;** 603:715–20.
31. Morens DM, Fauci AS. Emerging pandemic diseases: how we got to COVID-19. Cell **2020;** 182:1077–92.
32. Gottlieb M, Wang R, Yu H, et al. Severe fatigue and persistent symptoms at three months following SARS-CoV-2 infections during the Pre-Delta, Delta, and Omicron time periods: a multicenter prospective cohort study. Clin Infect Dis. **In press**.
33. Link-Gelles R, Levy ME, Gaglani M, et al. Effectiveness of 2, 3, and 4 COVID-19 mRNA vaccine doses among immunocompetent adults during periods when SARS-CoV-2 Omicron BA.1 and BA.2/BA.2.12.1 sublineages predominated—VISION network, 10 states, December 2021-June 2022. MMWR Morb Mortal Wkly Rep **2022;** 71:931–9.
34. Smith DJ, Hakim AJ, Leung GM, et al. COVID-19 mortality and vaccine coverage—Hong Kong special administrative region, China, January 6, 2022-March 21, 2022. MMWR Morb Mortal Wkly Rep **2022;** 71:545–8.