



Published in final edited form as:

Clin Infect Dis. 2024 February 17; 78(2): 338–348. doi:10.1093/cid/ciad505.

Clinical Epidemiology and Risk Factors for Critical Outcomes Among Vaccinated and Unvaccinated Adults Hospitalized With COVID-19—VISION Network, 10 States, June 2021–March 2023

Eric P. Griggs^{1,a}, Patrick K. Mitchell^{2,a}, Victoria Lazariu^{2,a}, Manjusha Gaglani^{3,4}, Charlene McEvoy⁵, Nicola P. Klein⁶, Nimish R. Valvi⁷, Stephanie A. Irving⁸, Noah Kojima⁹, Edward Stenehjem¹⁰, Bradley Crane⁸, Suchitra Rao¹¹, Shaun J. Grannis^{7,12}, Peter J. Embi¹³, Anupam B. Kharbanda¹⁴, Toan C. Ong¹¹, Karthik Natarajan^{15,16}, Kristin Dascomb¹⁰, Allison L. Naleway⁸, Elizabeth Bassett², Malini B. DeSilva⁵, Monica Dickerson⁹, Deepika Konatham¹⁷, Bruce Fireman⁶, Katie S. Allen^{7,18}, Michelle A. Barron¹¹, Maura Beaton¹⁵, Julie Arndorfer¹⁰, Gabriela Vazquez-Benitez⁵, Shikha Garg⁹, Kempapura Murthy¹⁷, Kristin Goddard⁶, Brian E. Dixon^{7,18}, Jungmi Han¹⁵, Nancy Grisel¹⁰, Chandni Raiyani¹⁷, Ned Lewis⁶, William F. Fadel^{7,18}, Melissa S. Stockwell^{19,20,21}, Mufaddal Mamawala¹⁷, John Hansen⁶, Ousseney Zerbo⁶, Palak Patel⁹, Ruth Link-Gelles¹, Katherine Adams^{9,b}, Mark W. Tenforde^{9,b}

¹Coronavirus and Other Respiratory Viruses Division, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia, USA;

²Department of Clinical Research, Westat, Inc, Rockville, Maryland, USA;

³Section of Pediatric Infectious Diseases, Department of Pediatrics, Baylor Scott & White Health, Temple, Texas, USA;

⁴Department of Medical Education, Texas A&M University College of Medicine, Temple, Texas, USA;

⁵Department of Research, HealthPartners Institute, Minneapolis, Minnesota, USA;

⁶Kaiser Permanente Vaccine Study Center, Division of Research, Kaiser Permanente Northern California, Oakland, USA;

⁷Center for Biomedical Informatics, Regenstrief Institute, Indianapolis, Indiana, USA;

⁸Department of Science Programs, Kaiser Permanente Center for Health Research, Portland, Oregon, USA;

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Correspondence: M. Tenforde, Influenza Division, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, 1600 Clifton Rd NE, MS H24-7, Atlanta, GA 30329 (pij6@cdc.gov).

^aE. P. G., P. K. M., and V. L. contributed equally to this work.

^bK. A. and M. W. T. contributed equally to this work as senior authors.

Supplementary Data

Supplementary materials are available at *Clinical 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.

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⁹Influenza Division, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia, USA;

¹⁰Division of Infectious Diseases and Clinical Epidemiology, Intermountain Healthcare, Salt Lake City, Utah, USA;

¹¹Department of Biomedical Informatics, School of Medicine, University of Colorado Anschutz Medical Campus, Aurora, Colorado, USA;

¹²Department of Family Medicine, School of Medicine, Indiana University, Indianapolis, Indiana, USA;

¹³Department of Biomedical Informatics, Vanderbilt University Medical Center, Nashville, Tennessee, USA;

¹⁴Department of Emergency Medicine, Children's Minnesota, Minneapolis, Minnesota, USA;

¹⁵Department of Biomedical Informatics, Columbia University Irving Medical Center, New York, New York, USA;

¹⁶Medical Informatics Services, New York–Presbyterian Hospital, New York, New York, USA;

¹⁷Department of Research Analytics and Development, Baylor Scott & White Research Institute, Baylor Scott & White Health, Temple, Texas, USA;

¹⁸Fairbanks School of Public Health, Indiana University, Indianapolis, Indiana, USA;

¹⁹Division of Child & Adolescent Health, Department of Pediatrics, New York–Presbyterian Hospital, New York, New York, USA;

²⁰Division of Child and Adolescent Health, Department of Pediatrics, Columbia University Vagelos College of Physicians and Surgeons, New York, New York, USA;

²¹Department of Population and Family Health, Columbia University Mailman School of Public Health, New York, New York, USA

Abstract

Background.—The epidemiology of coronavirus disease 2019 (COVID-19) continues to develop with emerging variants, expanding population-level immunity, and advances in clinical care. We describe changes in the clinical epidemiology of COVID-19 hospitalizations and risk factors for critical outcomes over time.

Methods.—We included adults aged ≥18 years from 10 states hospitalized with COVID-19 June 2021–March 2023. We evaluated changes in demographics, clinical characteristics, and critical outcomes (intensive care unit admission and/or death) and evaluated critical outcomes risk factors (risk ratios [RRs]), stratified by COVID-19 vaccination status.

Results.—A total of 60 488 COVID-19–associated hospitalizations were included in the analysis. Among those hospitalized, median age increased from 60 to 75 years, proportion vaccinated increased from 18.2% to 70.1%, and critical outcomes declined from 24.8% to 19.4% (all $P < .001$) between the Delta (June–December, 2021) and post-BA.4/BA.5 (September 2022–March 2023) periods. Hospitalization events with critical outcomes had a higher proportion of

4 categories of medical condition categories assessed (32.8%) compared to all hospitalizations (23.0%). Critical outcome risk factors were similar for unvaccinated and vaccinated populations; presence of 4 medical condition categories was most strongly associated with risk of critical outcomes regardless of vaccine status (unvaccinated: adjusted RR, 2.27 [95% confidence interval {CI}, 2.14–2.41]; vaccinated: adjusted RR, 1.73 [95% CI, 1.56–1.92]) across periods.

Conclusions.—The proportion of adults hospitalized with COVID-19 who experienced critical outcomes decreased with time, and median patient age increased with time. Multimorbidity was most strongly associated with critical outcomes.

Keywords

COVID-19; hospitalization; death; critical disease; clinical epidemiology

Approximately 6 million coronavirus disease 2019 (COVID-19)–associated hospitalizations and 1.1 million deaths have been reported in the United States (US) since 2020 [1]. During the early pandemic, factors associated with critical COVID-19 included advanced age and certain chronic medical conditions [2–4]. Less is known about the changing clinical epidemiology and risk factors for critical COVID-19 during recent variant periods.

With the emergence of new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants, rates of hospitalizations and case fatalities have changed [5–8]. This may be due to several factors, including increased population-level immunity following vaccination [9–11], infection-induced immunity [12–14], or “hybrid” immunity from both infection and vaccination. Adaptive changes of newer variants [15, 16] and broader use of therapies for acute COVID-19 [17–19] may also contribute. Given these dynamic changes, ongoing research is crucial to understand both the evolving epidemiology of COVID-19 and risk factors for critical outcomes among unvaccinated and vaccinated populations. Characterizing groups who remain at highest risk for critical outcomes is important to inform public health and clinical interventions targeting the most vulnerable populations.

The primary objective of this study was to explore the clinical profile of adults hospitalized with COVID-19 over time and identify risk factors associated with critical COVID-19 by vaccination status.

METHODS

Setting and Design

This study was conducted within the virtual SARS-CoV-2, influenza, and other respiratory viruses network (VISION), a multistate network that captures EHR data from healthcare systems with integrated laboratory, clinical, and vaccination records. VISION has performed serial evaluations of COVID-19 vaccine effectiveness since 2021 [20]. This analysis included adult patients (> 18 years of age) hospitalized at 8 healthcare systems in 10 US states (including 254 hospitals) from 1 June 2021 through 29 March 2023 (Supplementary Table 1). The analysis was reviewed and approved by institutional review boards at participating sites or under reliance agreement with the institutional review board of Westat.

All activities were conducted consistent with applicable federal law and Centers for Disease Control and Prevention (CDC) policy.

Study Population

We included adults hospitalized with COVID-19 during the period of Delta predominance (June 2021) through the post-BA.4/BA.5–predominant period including XBB sublineages (March 2023). Consistent with described methods [21], cases were patients with a COVID-19–associated hospitalization, defined as having 1 or more COVID-19–like illness *International Classification of Diseases, 10th Revision (ICD-10)* discharge codes and a positive molecular test for SARS-CoV-2 within 14 days before or up to 72 hours after admission. Pregnant patients were excluded due to differences in COVID-19 screening and testing practices and criteria for hospitalization. To characterize underserved populations, the CDC/Agency for Toxic Substances and Disease Registry Social Vulnerability Index (SVI) was included using geocoded data, as previously described [22].

Vaccination Status

COVID-19 vaccination status was determined using local immunization information systems, EHRs, and insurance claims and categorized as primary series only or primary series with additional doses of monovalent or updated bivalent messenger RNA (mRNA) boosters. mRNA vaccine doses received starting 2 September 2022 were considered bivalent [23]. Primary series completion was defined as documented receipt of 2 doses of an mRNA vaccine (BNT162b2 [Pfizer-BioNTech] and/or mRNA-1273 [Moderna]) or 1 dose of Ad26.COV2 (Janssen/Johnson & Johnson [J&J]) 14 days before the admission index date, defined as the date of respiratory specimen collection associated with the most recent SARS-CoV-2 test result prior to hospitalization or admission date if testing occurred following admission. For patients with immunocompromising conditions, completion of a primary series was defined as having received 3 doses of an mRNA vaccine or 1 dose of J&J followed by 1 additional mRNA dose [20]. Encounters among patients who received 1 or more doses of a COVID-19 vaccine but had not completed a primary series were excluded, as were those who received any sequence of vaccine products outside of the recommended schedules.

Classification of Variant-Predominant Periods

The study period began on the earliest day the Delta variant accounted for 50% of sequenced isolates at each site, based on local surveillance data, and ended when another variant accounted for 50% of sequenced isolates (Delta date range: 1 June–29 December 2021). Each subsequent variant/sublineage-predominant period was defined similarly (Omicron BA.1: 16 December 2021–30 March 2022; Omicron BA.2/BA.2.12.1: 17 March–29 June 2022; Omicron BA.4/BA.5: 19 June–29 October 2022; post–Omicron BA.4/BA.5: 29 October 2022–29 March 2023).

Outcome Classification

The primary outcome was “critical” COVID-19 outcomes, defined as a composite of hospitalization resulting in intensive care unit (ICU) admission and/or in-hospital death.

This endpoint was selected to reflect critical disease [24] while utilizing outcomes collected across all sites. Secondary critical outcomes, measured at a subset of partner sites, included any use of noninvasive mechanical ventilation (NMV, including bivalve positive airway pressure or continuous positive airway pressure), or invasive mechanical ventilation (IMV). Additional markers of critical illness described in the supplementary analyses included *ICD-10* codes indicating COVID-19–associated complications such as acute respiratory distress syndrome (ARDS), respiratory failure, and all-cause pneumonia.

Statistical Analysis

Baseline demographics, clinical characteristics, and outcomes were stratified by variant period and described using counts and percentages or medians and interquartile ranges (IQRs). Trends across periods were assessed using the Jonckheere-Terpstra nonparametric test [25] for continuous variables and ordered categorical variables with >2 groups, and the Cochran-Armitage [26, 27] test for binary variables.

Key characteristics (vaccination status, age ≥ 65 years, ≥ 4 underlying medical condition [UMC] categories) of patients with critical outcomes were visualized by period using Euler diagrams, with the size of ellipses representing the proportion of patients with each characteristic and overlap between ellipses representing co-presence of characteristics. Counts of COVID-19 hospitalizations and proportions with critical outcomes (primary outcomes of ICU admission and/or in-hospital death, secondary outcomes including NMV and/or IMV) were graphed by week.

We evaluated risk factors for critical outcomes overall (ie, across all study periods) and during each variant period separately for both unvaccinated and vaccinated (primary series or more) populations. Due to the similar characteristics and outcomes among patients with critical outcomes during the BA.2, BA.4/BA.5, and post-BA.4/BA.5 periods, we collapsed these into 1 post-BA.1 period. A modified Poisson regression approach through a generalized linear model with robust error variance [28] was used to estimate adjusted risk ratios (aRRs), accounting for potential confounders including patient characteristics (age, sex, race, Hispanic ethnicity, Medicaid status), UMCs (number of condition categories or by individual conditions), and facility characteristics (VISION site, hospital size, hospital type, urban/rural classification). Addition of calendar time was also considered but had little influence on risk ratio estimates. UMCs were defined using *ICD-10* discharge codes for the index encounter and assumed to be baseline conditions predating hospitalization, although the chronicity of conditions or new-onset diagnoses associated with the index hospitalization could not be definitively determined. Condition categories included respiratory (asthma, chronic obstructive pulmonary disease [COPD]), cardiovascular (heart failure, ischemic heart disease, hypertension, congenital heart disease), cerebrovascular (stroke, other), neurological/musculoskeletal (dementia, Down syndrome, other), endocrine/metabolic (diabetes, other), hematologic, renal, hepatic, or immunocompromising conditions (Supplementary Table 2). Among vaccinated, risk ratios were also adjusted for whether the patient had completed a primary vaccine series or a primary vaccine series plus 1 or more booster doses; other specifications, including models also adjusting for time since most recent dose or number of booster doses, generated similar findings. Depending on

the risk factor, 1 of 2 regression models was run to assess UMCs. In the first model, a categorical variable counting the number of system categories affected was included as an independent variable. For the second model, individual indicators of each UMC were included as independent variables. Analyses were conducted using R software (version 4.1.2; R Foundation).

RESULTS

Characteristics of Hospitalized Patients Across Predominant Periods

Of 66 166 COVID-19–associated hospitalizations in nonpregnant adults during the study period, 5678 (8.6%) were excluded due to being partially vaccinated ($n = 5382$), receiving vaccines outside of recommended schedules ($n = 294$), or receiving a vaccine product other than Janssen, Moderna, or Pfizer ($n = 2$), leaving 60 488 eligible hospitalizations. Median age of patients was 67 years (IQR, 54–79 years), 31 230 (51.6%) were male, 41 893 (69.3%) were White, and 42 728 (70.6%) were non-Hispanic (Table 1). Of patients with geocoded information on place of residence, 19.5% were in the highest SVI quartile. The median number of UMC categories was 2 (IQR, 1–3), with 8021 (13.3%) patients having an immunocompromising condition.

Age at hospitalization increased across periods, with a median of 60 years (IQR, 48–72 years) during Delta and 75 years (IQR, 65–84 years) during post-BA.4/BA.5 ($P < .001$) (Table 1). The proportion of patients with 4 UMC categories increased from 13.4% during Delta to 31.6% during post-BA.4/5 ($P < .001$). The proportion vaccinated with at least a primary series increased from 18.2% during Delta to 70.1% during post-BA.4/BA.5 ($P < .001$).

Characteristics of Patients With Critical COVID-19 Outcomes and Trends Across Predominant Periods

Overall, 13 536 (22.4%) hospitalizations included critical outcomes (Table 2), with 11 408 (18.9%) ICU admissions and 5708 (9.4%) deaths (Supplementary Table 3). The proportion of patients with critical outcomes was highest during the Delta period (Supplementary Table 3; Figure 1). Overall, 4751 of 33 411 (14.2%) hospitalizations required NMV and 5171 of 48 441 (10.7%) required IMV. Demographic characteristics of patients with critical outcomes followed similar patterns as all COVID-19 hospitalizations. Compared with all hospitalized patients, a greater proportion of those with critical illness had 4 UMC categories (32.8% vs 23.0%) and immunocompromising conditions (17.9% vs 13.3%), and a lower proportion were vaccinated with at least a primary series (34.9% vs 41.9%).

The proportion of patients with critical outcomes who were older (> 65 years) and had 4 UMC categories increased across periods ($P < .001$), while the unvaccinated proportion decreased ($P < .001$) (Table 2, Figure 2). The overall proportion of ICU admissions and in-hospital deaths declined across periods ($P < .001$) (Figure 1; Supplementary Table 3). These trends were consistent across secondary outcomes such as ARDS, NMV, and IMV ($P < .001$) (Supplementary Table 3, Supplementary Figure 1). Hospital length of stay decreased across periods for patients with critical outcomes who survived (ie, admitted and discharged

from ICU), with a median of 5 days (IQR, 3–10 days) during Delta and 4 days (IQR, 3–7 days) during post-BA.4/BA.5 ($P < .001$). However, length of stay also decreased among in-hospital deaths, with a median of 11 days (IQR, 6–22 days) during Delta and 7 days (IQR, 4–14 days) during post-BA.4/BA.5 ($P < .001$).

Risk Factors for Critical Outcomes Across Predominant Periods

Adjusting for UMCs and other factors, during the Delta period age >49 years was associated with an increased risk of critical outcomes (Figure 3 and 4). During later periods, however, the adjusted risk of critical outcomes was lower in older versus young adults. During the Delta period, adults aged 18–49 years comprised 32.8% of unvaccinated and 6.9% of vaccinated patients, whereas during the post-BA.1 period young adults comprised 16.5% of unvaccinated and 7.0% of vaccinated patients. Female sex was associated with a reduced risk of critical outcomes across periods (aRR, 0.82 and 0.85 in unvaccinated and vaccinated, respectively).

Patients with ≥ 4 UMCs were at an increased risk for ICU admission and/or death across all periods in both unvaccinated (overall aRR, 2.27 [95% confidence interval {CI}, 2.14–2.41]) and vaccinated (overall aRR, 1.73 [95% CI, 1.56–1.92]) groups. Presence of 2–3 UMCs was also a risk factor across multiple periods for unvaccinated, but with a lower relative strength of association. Most categories of UMCs were associated with a modest increase in risk of critical outcomes (aRR >1.0) across periods in both unvaccinated (Figure 3) and vaccinated (Figure 4) adults.

In a secondary analysis evaluating risk factors for severe respiratory illness (NMV and/or IMV), similar results were observed as in the primary analysis, although the magnitude of effect size such as for multiple UMCs was higher and an association between older age and lower independent risk of critical illness was observed across periods (Supplementary Figures 2A and 2B).

Visualizing the relationship between categories of UMCs and critical outcomes, the proportion of patients with a critical outcome increased as the number of UMC categories increased across all periods (Supplementary Figure 3). The most common combinations of UMC categories for patients with ≥ 4 categories included cardiovascular, neurological or musculoskeletal, endocrine or metabolic, and renal (Supplementary Table 4).

DISCUSSION

Among adults hospitalized across 10 states between June 2021 and March 2023, the epidemiology of COVID-19 changed markedly. Over time, the overall proportion of ICU admissions, in-hospital deaths, use of noninvasive or invasive mechanical ventilation or ARDS, and length of stay decreased. Changes in baseline patient characteristics included an increase in median age of 15 years across the study period and a majority of those with COVID-19–associated hospitalizations now having been vaccinated against COVID-19 as population-level coverage expanded. Among both unvaccinated and vaccinated patients, a high burden of UMCs was the strongest predictor of ICU admission and/or death. A small number of factors, including vaccination status, high burden of UMCs, and advanced age,

identified a vast majority of patients who experienced critical outcomes (90%–97% across periods), suggesting target populations for future public health and clinical efforts.

Adjusting for confounders, clinical risk factors for critical COVID-19 outcomes were similar over time between unvaccinated and vaccinated patients. Regardless of vaccination status, the presence of UMCs across multiple organ system categories was the strongest risk factor for critical disease. This suggests that overall frailty may play a larger role in susceptibility to critical disease than a singular diagnosis. Notably, we captured general condition categories, and within a single category (eg, immunocompromising conditions) there may be a gradient of risk. While VISION does not collect data on how well-controlled UMCs are, ongoing management of UMCs may minimize complications associated with COVID-19 [29]. Future studies should evaluate risk of critical outcomes accounting for severity or level of control of underlying conditions to provide greater understanding.

Various medical conditions and age have been consistently associated with an increased risk of severe COVID-19 illness from previous studies [30–32]. In our analysis, older adults were overrepresented among both total hospitalizations and severe hospitalizations across periods, and older age was associated with an increased risk of critical outcomes (ICU admission or death) during the Delta variant period. This association was reversed, however, during the post-BA.1 period, with older adults hospitalized with COVID-19 at lower risk for critical outcomes adjusting for UMCs and other confounders. These findings may be attributable to several factors, including a lower threshold for SARS-CoV-2 testing and admission for less severe disease in older adults, residual confounding based on types or severity of medical conditions or unmeasured factors, differential use of early antiviral therapies across ages, advanced directives or goals of in-hospital care in older adults, or differences in the clinical presentation of illness by age. For example, older adults may be more likely to be hospitalized due to exacerbation of chronic medical conditions associated with SARS-CoV-2 infection rather than primary viral pneumonia. Inclusion in this analysis was also conditioned on hospitalization, and older adults in institutional settings (eg, skilled nursing facilities) likely to have poor outcomes may not have been hospitalized. Regardless, the average age and proportion of older adults hospitalized with COVID-19 increased over time, highlighting that the greatest burden of critical COVID-19 outcomes is experienced among older adults.

Compared with all hospitalized patients, a lower proportion of patients with critical COVID-19 outcomes were vaccinated with at least a primary vaccination series; however, the severity of disease among both vaccinated and unvaccinated populations declined over time. These data support that COVID-19 severity declined during Omicron variant predominance [33, 34]. Risk of critical illness may have been attenuated by vaccination [9], the increased prevalence of immunity induced by prior SARS-CoV-2 infection [35, 36], changes in aspects of the predominant SARS-CoV-2 variant [37], or changes in clinical management [17–19].

This analysis was subject to limitations. First, as eligible encounters occurred across multiple variant periods, clinical management may have changed. Data on treatments such as antivirals were not captured by VISION partners throughout the study period, limiting

our ability to assess the impact of changing therapeutic practices. Second, prior infection was unable to be reliably ascertained from available testing data, complicating interpretation of conclusions that aim to disentangle the contribution of vaccine-induced immunity and infection-induced immunity. Third, we could not reliably capture whether a patient with COVID-19–like illness and a positive SARS-CoV-2 test was admitted primarily because of COVID-19 or due to other contributing conditions. EHR data may also not fully capture all UMCs and could result in misclassification of higher-risk patients and underreporting of intensive care received, particularly during periods of high incidence of SARS-CoV-2 infections when non-ICU beds were used for critically ill patients [38, 39]. Fourth, these findings are from data collected in 10 states and may not be generalizable to the entire US population. Due to the absence of comprehensive national integrated systems across a representative population, networks like VISION rely on health systems that capture robust and integrated clinical, laboratory, and vaccination information. Furthermore, as our study population is patients already hospitalized with COVID-19, our findings are not intended to reflect a wider population outside the hospital setting. Fifth, our primary severity outcomes of ICU admission and/or in-hospital death are not specific to COVID-19. Sixth, chronicity of medical conditions was not assessed. While documented conditions such as diabetes and COPD are likely to represent chronic conditions, it is possible that some conditions included new-onset diagnoses or may have resulted from COVID-19. Encounter-based reporting of conditions may be incomplete without a lookback period predating admission; additional information including capture of all vaccine doses may also be incomplete.

In conclusion, from the Delta-predominant period to the post-BA.4/BA.5 period, the epidemiology of COVID-19 among hospitalized patients changed markedly. Over time, the proportion of ICU admissions, in-hospital deaths, use of NMV and IMV, and hospital length of stay decreased. However, in all periods the majority of hospitalizations resulting in ICU admission or death among both vaccinated and unvaccinated patients were among patients who were older (> 65 years) or had multiple underlying medical conditions. Continued research is needed to understand the changing epidemiology of COVID-19 hospitalizations with the emergence of new SARS-CoV-2 variants or sublineages, changes in population-level immunity, and development of new vaccines and therapies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Financial support.

This work was supported by the Centers for Disease Control and Prevention (contract number 75D30120C07986 to Westat and contract number 75D30120C07765 to Kaiser Foundation Hospitals).

Potential conflicts of interest.

M. G. reports additional grants or institutional contracts with the CDC Ambulatory US Flu/COVID Vaccine Effectiveness (VE) Network, Hospitalized Adult Influenza Vaccine Effectiveness Network (HAIVEN) Adult Inpatient Flu/COVID VE, Investigating Respiratory Viruses in the Acutely Ill Public Health Surveillance Network, and Researching COVID to Enhance Recovery and Health and Human Services Protect. C. M. reports an institutional grant or contract from AstraZeneca (AZD1222) for a COVID-19 vaccination trial. A. L. N. reports institutional research funding from Pfizer for an unrelated study of meningococcal B vaccine safety during pregnancy and Vir Biotechnology for an unrelated influenza study. S. A. I. reports an additional pending contract

with CDC (200-2012-53584, Vaccine Safety Datalink). G. V.-B. reports grants or contracts from CDC (Vaccine Safety Datalink) and Sanofi (Tdap Vaccine Safety). A. B. K. reports a sub-contract through HealthPartners for VISION payment made to Children's Minnesota. B. E. D. reports a grant from the National Institutes of Health to evaluate Health Information Exchange (HIE) technologies, a grant from CDC to use HIE data for public health surveillance, an R21 grant from the US Agency for Healthcare Research and Quality to evaluate HIE technologies, a grant from the US Department of Veterans Affairs to evaluate HIE technologies, royalties from Elsevier and Springer Nature for books on HIE and public health informatics, and consulting fees for advisory panel on human papillomavirus vaccination from Merck and Co. K. M. reports 2 additional contracts with CDC (Ambulatory US Flu VE Network and HAIVEN). N. P. K. has received grants from Pfizer, Merck, GlaxoSmithKline, and Sanofi Pasteur. S. R. has received grant funds from GlaxoSmithKline. P. K. M., V. L., and E. B. report payments made to Westat via CDC (contract number 200-2019-F-06819). C. M., C. R., D. K., E. S., G. V.-B., J. A., J. Han., K. S. A., K. N., K. D., M. B., M. B. D., M. M., M. S. S., N. G., N. R. V., P. J. E., S. G., T. C. O., and W. F. F. report payments made to their institution by CDC via Westat. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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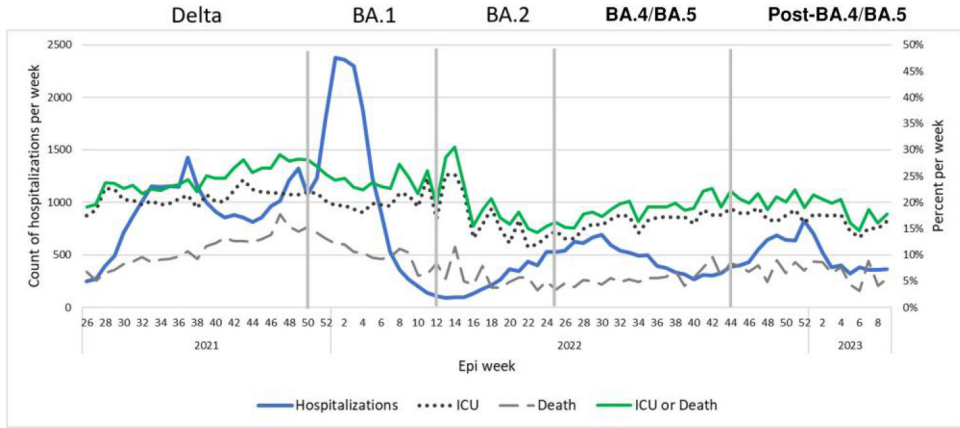


Figure 1. Weekly numbers of adults with coronavirus disease 2019–associated hospitalizations and percentage with an intensive care unit (ICU) admission and/or in-hospital death across 4 variant-predominant periods, VISION Network, 27 June 2021–4 March 2023. Data are included starting on Centers for Disease Control and Prevention epidemiological surveillance week (Epi week) 26 in 2021 (beginning 27 June) and ends on Epi week 9 in 2023 (through 4 March); however, data from Baylor Scott & White Health are included starting on Epi week 36 (11 September 2021).

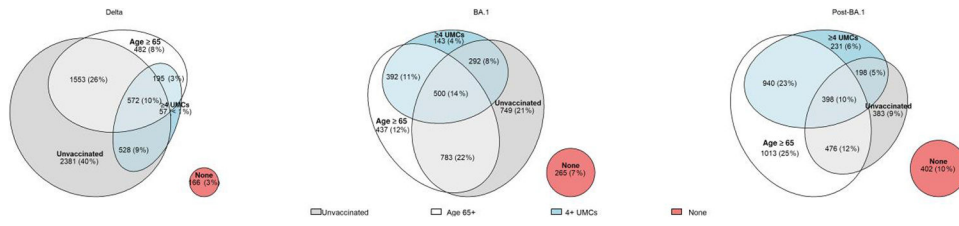


Figure 2. Visualization of select characteristics of adults with an intensive care unit admission and/or in-hospital death by Delta and Omicron sublineage–predominant periods, VISION Network, 1 June 2021–29 March 2023. Abbreviation: UMCs, underlying medical conditions (by number of categories).

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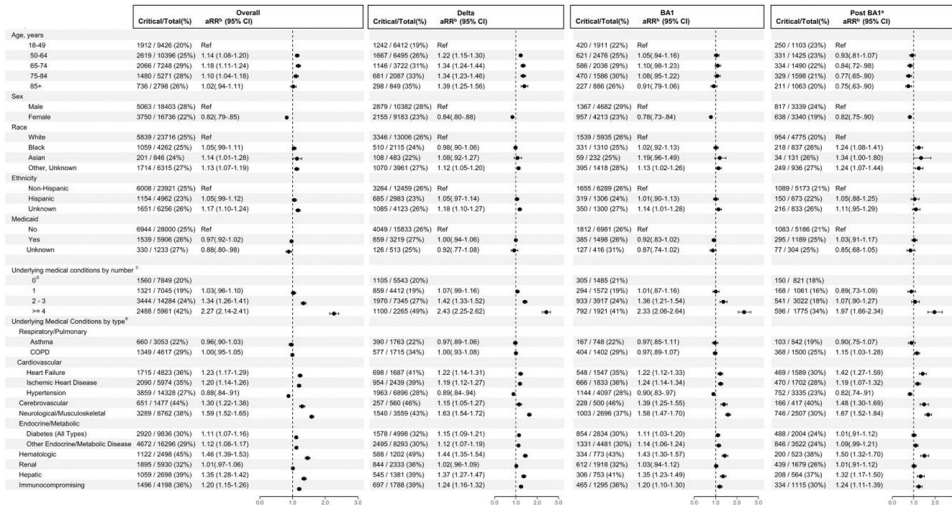


Figure 3. Risk factors for intensive care unit admission and/or in-hospital death by Delta and Omicron sublineage-predominant periods among unvaccinated adults, VISION Network, 1 June 2021–29 March 2023. ^aPost-BA.1 includes BA.2, BA.4, BA.5, and post-BA.5. ^bAdjusted for age, sex, race, Hispanic ethnicity, Medicaid status, underlying medical conditions (UMCs; number of medical conditions and by individual conditions), and facility characteristics (VISION Network partner, hospital size, hospital type, urban/rural classification). ^cEstimated from a model containing background variables and number of UMC categories. Categories of UMCs include pulmonary, cardiovascular, cerebrovascular, neurological or musculoskeletal, endocrine or metabolic, hematologic, renal, hepatic, and immunocompromising condition. ^dReference group. ^eReference for UMC is no presence of condition. Abbreviations: aRR, adjusted risk ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease.

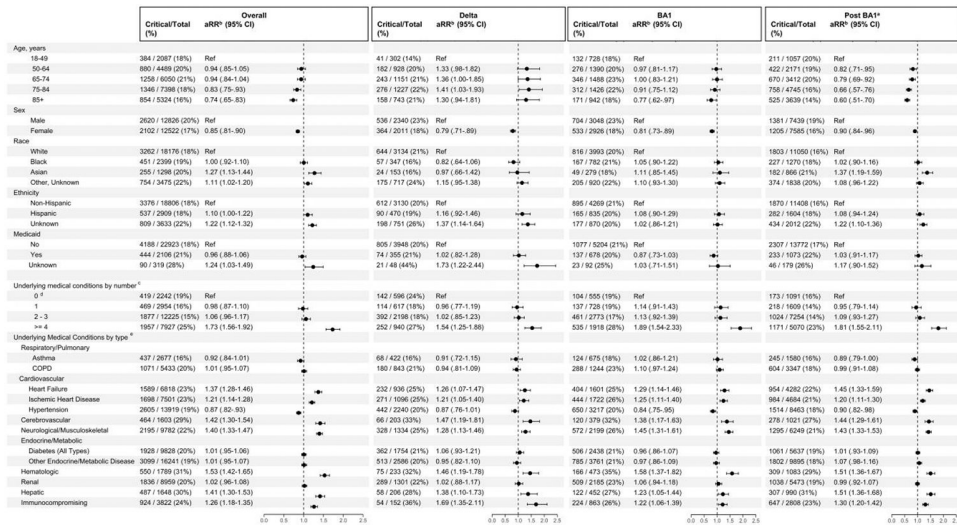


Figure 4. Risk factors for intensive care unit admission and/or in-hospital death by Delta and Omicron sublineage–predominant periods among vaccinated adults, VISION Network, 1 June 2021–29 March 2023. ^aIncludes BA.2, BA.4, BA.5, and post-BA.5. ^bAdjusted for age, sex, race, Hispanic ethnicity, Medicaid status, underlying medical conditions (UMCs; number of medical conditions and by individual conditions), facility characteristics (VISION Network partner, hospital size, hospital type, urban/rural classification), and primary series versus primary series plus 1 or more boosters. ^cEstimated from a model containing background variables and number of UMC categories. Categories of UMCs include pulmonary, cardiovascular, cerebrovascular, neurological or musculoskeletal, endocrine or metabolic, hematologic, renal, hepatic, and immunocompromising condition. ^dReference group. ^eReference for UMC is no presence of condition. Abbreviations: aRR, adjusted risk ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease.

Table 1. Characteristics of Adults Hospitalized With Coronavirus Disease 2019 by Delta and Omicron Sublineage–Predominant Periods, VISION Network, 1 June 2021–29 March 2023

Characteristic	Overall	Variant-Predominant Period ^a					P Value ^b
		Delta	BA.1	BA.2	BA.4/BA.5	Post-BA.4/BA.5	
All hospitalizations, No.	60 488	23 916	14 869	3549	8655	9499	
Age, y, median (IQR)	67 (54–79)	60 (48–72)	67 (55–78)	75 (63–83)	74 (63–83)	75 (65–84)	<.001
Age, y							<.001
18–49	11 513 (19.0)	6714 (28.1)	2639 (17.7)	395 (11.1)	952 (11.0)	813 (8.6)	
50–64	14 885 (24.6)	7423 (31.0)	3866 (26.0)	603 (17.0)	1498 (17.3)	1495 (15.7)	
65–74	13 299 (22.0)	4873 (20.4)	3524 (23.7)	749 (21.1)	1985 (22.9)	2168 (22.8)	
75–84	12 669 (20.9)	3314 (13.9)	3012 (20.3)	1032 (29.1)	2451 (28.3)	2860 (30.1)	
85	8122 (13.4)	1592 (6.7)	1828 (12.3)	770 (21.7)	1769 (20.4)	2163 (22.8)	
Sex							
Male	31 230 (51.6)	12 722 (53.2)	7730 (52.0)	1786 (50.3)	4311 (49.8)	4681 (49.3)	<.001
Female	29 258 (48.4)	11 194 (46.8)	7139 (48.0)	1763 (49.7)	4344 (50.2)	4818 (50.7)	<.001
Race							
White	41 893 (69.3)	16 140 (67.5)	9928 (66.8)	2587 (72.9)	6292 (72.7)	6946 (73.1)	<.001
Black	6661 (11.0)	2462 (10.3)	2092 (14.1)	315 (8.9)	903 (10.4)	889 (9.4)	<.001
Asian	2144 (3.5)	636 (2.7)	511 (3.4)	218 (6.1)	355 (4.1)	424 (4.5)	<.001
Other/unknown	9790 (16.2)	4678 (19.6)	2338 (15.7)	429 (12.1)	1105 (12.8)	1240 (13.1)	<.001
Ethnicity							
Non-Hispanic	42 728 (70.6)	15 589 (65.2)	10 558 (71.0)	2753 (77.6)	6612 (76.4)	7216 (76.0)	<.001
Hispanic	7871 (13.0)	3453 (14.4)	2141 (14.4)	345 (9.7)	885 (10.2)	1047 (11.0)	<.001
Unknown	9889 (16.3)	4874 (20.4)	2170 (14.6)	451 (12.7)	1158 (13.4)	1236 (13.0)	<.001
SVI quartile ^c							.002
Q1	10 526 (30.5)	4149 (30.3)	2452 (27.5)	608 (35.2)	1570 (31.1)	1747 (34.1)	
Q2	9440 (27.3)	3894 (28.4)	2340 (26.2)	460 (26.7)	1381 (27.4)	1365 (26.6)	
Q3	7820 (22.6)	3100 (22.6)	2076 (23.3)	393 (22.8)	1138 (22.6)	1113 (21.7)	
Q4	6740 (19.5)	2571 (18.7)	2049 (23.0)	264 (15.3)	952 (18.9)	904 (17.6)	
Categories of UMCs, median (IQR) ^d	2 (1–3)	2 (0–3)	2 (1–4)	3 (2–4)	3 (2–4)	3 (2–4)	<.001

Characteristic	Variant-Predominant Period ^a						P Value ^b
	Overall	Delta	BA.1	BA.2	BA.4/BA.5	Post-BA.4/BA.5	
Categories of UMCs, by number ^d							<.001
0	10 091 (16.7)	6139 (25.7)	2040 (13.7)	282 (7.9)	793 (9.2)	837 (8.8)	
1	9999 (16.5)	5029 (21.0)	2300 (15.5)	443 (12.5)	1078 (12.5)	1149 (12.1)	
2-3	26 509 (43.8)	9543 (39.9)	6690 (45.0)	1649 (46.5)	4119 (47.6)	4508 (47.5)	
4	13 889 (23.0)	3205 (13.4)	3839 (25.8)	1175 (33.1)	2665 (30.8)	3005 (31.6)	
UMC, by type							
Respiratory/pulmonary	15 155 (25.1)	4610 (19.3)	3902 (26.2)	1133 (31.9)	2605 (30.1)	2905 (30.6)	<.001
Asthma	5730 (9.5)	2185 (9.1)	1423 (9.6)	406 (11.4)	819 (9.5)	897 (9.4)	.196
COPD	10 051 (16.6)	2558 (10.7)	2646 (17.8)	773 (21.8)	1912 (22.1)	2162 (22.8)	<.001
Nonrespiratory/nonpulmonary	48 926 (80.9)	17 136 (71.7)	12 512 (84.1)	3202 (90.2)	7655 (88.4)	8421 (88.7)	<.001
Cardiovascular	33 432 (55.3)	10 699 (44.7)	8709 (58.6)	2307 (65.0)	5511 (63.7)	6206 (65.3)	<.001
Heart failure	11 642 (19.2)	2623 (11.0)	3148 (21.2)	985 (27.8)	2238 (25.9)	2648 (27.9)	<.001
Ischemic heart disease	13 476 (22.3)	3535 (14.8)	3555 (23.9)	1043 (29.4)	2432 (28.1)	2911 (30.6)	<.001
Hypertension	28 248 (46.7)	9136 (38.2)	7314 (49.2)	1939 (54.6)	4680 (54.1)	5179 (54.5)	<.001
Congenital heart disease	314 (0.5)	97 (0.4)	98 (0.7)	14 (0.4)	49 (0.6)	56 (0.6)	.055
Cerebrovascular	3080 (5.1)	763 (3.2)	879 (5.9)	242 (6.8)	566 (6.5)	630 (6.6)	<.001
Stroke	1455 (2.4)	422 (1.8)	463 (3.1)	84 (2.4)	224 (2.6)	262 (2.8)	<.001
Other cerebrovascular disease	1907 (3.2)	405 (1.7)	509 (3.4)	179 (5.0)	388 (4.5)	426 (4.5)	<.001
Neurological/musculoskeletal	18 544 (30.7)	4893 (20.5)	4895 (32.9)	1424 (40.1)	3423 (39.5)	3909 (41.2)	<.001
Dementia	5355 (8.9)	929 (3.9)	1412 (9.5)	486 (13.7)	1184 (13.7)	1344 (14.1)	<.001
Other neuromuscular	16 178 (26.7)	4446 (18.6)	4305 (29.0)	1181 (33.3)	2931 (33.9)	3315 (34.9)	<.001
Down syndrome	87 (0.1)	44 (0.2)	24 (0.2)	1 (0.0)	9 (0.1)	9 (0.1)	.014
Endocrine/metabolic	37 351 (61.7)	12 904 (54.0)	9500 (63.9)	2492 (70.2)	5900 (68.2)	6555 (69.0)	<.001
Diabetes (all types)	19 665 (32.5)	6752 (28.2)	5272 (35.5)	1294 (36.5)	2984 (34.5)	3363 (35.4)	<.001
Other endocrine/metabolic disease	32 538 (53.8)	10 879 (45.5)	8242 (55.4)	2242 (63.2)	5294 (61.2)	5881 (61.9)	<.001
Hematologic	4287 (7.1)	1435 (6.0)	1246 (8.4)	294 (8.3)	631 (7.3)	681 (7.2)	<.001
Renal	14 889 (24.6)	3634 (15.2)	4103 (27.6)	1207 (34.0)	2775 (32.1)	3170 (33.4)	<.001
Hepatic	4346 (7.2)	1587 (6.6)	1205 (8.1)	256 (7.2)	653 (7.5)	645 (6.8)	.39
Immunocompromising condition	8021 (13.3)	1940 (8.1)	2158 (14.5)	659 (18.6)	1587 (18.3)	1677 (17.7)	<.001
COVID-19 vaccination status							<.001

Characteristic	Variant-Predominant Period ^a						P Value ^b
	Overall	Delta	BA.1	BA.2	BA.4/BA.5	Post-BA.4/BA.5	
Unvaccinated	35 139 (58.1)	19 565 (81.8)	8895 (59.8)	1055 (29.7)	2782 (32.1)	2842 (29.9)	
Completed primary series	14 540 (24.0)	4170 (17.4)	4653 (31.3)	1101 (31.0)	2343 (27.1)	2273 (23.9)	
Primary series + 1 booster dose (1st booster)	7680 (12.7)	177 (0.7)	1304 (8.8)	1216 (34.3)	2595 (30.0)	2388 (25.1)	
Primary series + 2 booster doses (1st & 2nd booster)	2418 (4.0)	4 (0.0)	16 (0.1)	176 (5.0)	902 (10.4)	1320 (13.9)	
Primary series + 3 booster doses (1st, 2nd, & 3rd booster)	703 (1.2)	0 (0.0)	1 (0.0)	1 (0.0)	33 (0.4)	668 (7.0)	
Primary series + 4 booster doses (1st, 2nd, 3rd & 4th booster)	8 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	8 (0.1)	
Any bivalent dose ^c	1660 (2.7)	0 (0.0)	0 (0.0)	0 (0.0)	93 (1.1)	1567 (16.5)	<.001
SARS-CoV-2 infection and related factors							
Historical positive test (pre-Omicron)	2159 (3.6)	446 (1.9)	539 (3.6)	172 (4.8)	443 (5.1)	559 (5.9)	<.001
Historical positive test (Omicron)	1932 (3.2)	0 (0.0)	337 (2.3)	184 (5.2)	611 (7.1)	800 (8.4)	<.001

Data are presented as No. (column %) unless otherwise indicated.

Abbreviations: COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; IQR, interquartile range; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SVI, Social Vulnerability Index; UMC, underlying medical condition.

^aDelta: 1 June–29 December 2021; Omicron BA.1: 16 December 2021–30 March 2022; Omicron BA.2/BA.2.12.1: 17 March–29 June 2022; Omicron BA.4/BA.5: 19 June–29 October 2022; post-Omicron BA.5: 29 October 2022–29 March 2023.

^bThe Cochran-Armitage test was used for binary variables and the Jonckheere-Terpstra test was performed for continuous and ordered categorical variables with >2 groups. Categories of race and ethnicity were treated as binary (yes/no) variables with individual *P* values presented.

^cSVI was not available for 25 962 (42.9%) encounters. Two sites contributing 15 030 (24.8%) encounters had no SVI data available and SVI data were missing for 10 932 (24.0%) encounters from the remaining sites.

^dCategories of UMCs include respiratory or pulmonary, cardiovascular, cerebrovascular, neurological or musculoskeletal, endocrine or metabolic, hematologic, renal, hepatic, and immunocompromising conditions.

^eAny mRNA vaccine doses received on or after 2 September 2022 were considered to be bivalent.

Table 2. Characteristics of Adults With an Intensive Care Unit Admission and/or In-Hospital Death by Delta and Omicron Sublineage—Predominant Periods, VISION Network, 1 June 2021–29 March 2023

Characteristic	Overall	Variant-Predominant Period ^a					P Value ^b
		Delta	BA.1	BA.2	BA.4/BA.5	Post-BA.4/BA.5	
All patients with critical outcomes, No.	13 536	5934	3561	612	1590	1839	
Age, y, median (IQR)	67 (56–78)	63 (51.25–74)	68 (57–78)	72 (60–82)	72 (61–81)	74 (63–83)	<.001
Age, y							<.001
18–49	2296 (17.0)	1283 (21.6)	552 (15.5)	74 (12.1)	212 (13.3)	175 (9.5)	
50–64	3499 (25.8)	1849 (31.2)	897 (25.2)	125 (20.4)	306 (19.2)	322 (17.5)	
65–74	3325 (24.6)	1389 (23.4)	932 (26.2)	150 (24.5)	393 (24.7)	461 (25.1)	
75–84	2826 (20.9)	957 (16.1)	782 (22.0)	146 (23.9)	430 (27.0)	511 (27.8)	
85	1590 (11.7)	456 (7.7)	398 (11.2)	117 (19.1)	249 (15.7)	370 (20.1)	
Sex							
Male	7684 (56.8)	3415 (57.5)	2071 (58.2)	346 (56.5)	894 (56.2)	958 (52.1)	<.001
Female	5852 (43.2)	2519 (42.5)	1490 (41.8)	266 (43.5)	696 (43.8)	881 (47.9)	<.001
Race							
White	9102 (67.2)	3990 (67.2)	2355 (66.1)	427 (69.8)	1067 (67.1)	1263 (68.7)	.254
Black	1510 (11.2)	567 (9.6)	498 (14.0)	61 (10.0)	208 (13.1)	176 (9.6)	.248
Asian	456 (3.4)	132 (2.2)	108 (3.0)	36 (5.9)	82 (5.2)	98 (5.3)	<.001
Other/unknown	2468 (18.2)	1245 (21.0)	600 (16.8)	88 (14.4)	233 (14.7)	302 (16.4)	<.001
Ethnicity							
Non-Hispanic	9385 (69.3)	3876 (65.3)	2550 (71.6)	458 (74.8)	1187 (74.7)	1314 (71.5)	<.001
Hispanic	1691 (12.5)	775 (13.1)	484 (13.6)	60 (9.8)	151 (9.5)	221 (12.0)	.002
Unknown	2460 (18.2)	1283 (21.6)	527 (14.8)	94 (15.4)	252 (15.8)	304 (16.5)	<.001
SVI quartile ^c							.4
Q1	2229 (28.2)	1021 (29.5)	535 (24.6)	107 (34.5)	258 (27.9)	308 (30.2)	
Q2	2165 (27.4)	959 (27.7)	595 (27.4)	74 (23.9)	265 (28.6)	272 (26.6)	
Q3	1821 (23.1)	775 (22.4)	532 (24.5)	79 (25.5)	205 (22.1)	230 (22.5)	
Q4	1680 (21.3)	708 (20.4)	513 (23.6)	50 (16.1)	198 (21.4)	211 (20.7)	
Categories of UMCs, median (IQR) ^d	3 (1–4)	2 (1–3)	3 (2–4)	3 (2–4)	3 (2–4)	3 (2–4)	<.001

Characteristic	Variant-Predominant Period ^e						P Value ^b
	Overall	Delta	BA.1	BA.2	BA.4/BA.5	Post-BA.4/BA.5	
Categories of UMCs, by number ^d							<.001
0	1979 (14.6)	1247 (21.0)	409 (11.5)	42 (6.9)	128 (8.1)	153 (8.3)	
1	1790 (13.2)	973 (16.4)	431 (12.1)	61 (10.0)	150 (9.4)	175 (9.5)	
2-3	5321 (39.3)	2362 (39.8)	1394 (39.1)	251 (41.0)	639 (40.2)	675 (36.7)	
4	4446 (32.8)	1352 (22.8)	1327 (37.3)	258 (42.2)	673 (42.3)	836 (45.5)	
UMCs, by type							
Respiratory/pulmonary	3379 (25.0)	1183 (19.9)	941 (26.4)	209 (34.2)	466 (29.3)	580 (31.5)	<.001
Asthma	1097 (8.1)	458 (7.7)	291 (8.2)	61 (10.0)	133 (8.4)	154 (8.4)	.213
COPD	2421 (17.9)	757 (12.8)	692 (19.4)	153 (25.0)	360 (22.6)	459 (25.0)	<.001
Nonrespiratory/nonpulmonary	11 316 (83.6)	4577 (77.1)	3090 (86.8)	560 (91.5)	1445 (90.9)	1644 (89.4)	<.001
Cardiovascular	8050 (59.5)	2999 (50.5)	2278 (64.0)	412 (67.3)	1077 (67.7)	1284 (69.8)	<.001
Heart failure	3305 (24.4)	930 (15.7)	952 (26.7)	207 (33.8)	552 (34.7)	664 (36.1)	<.001
Ischemic heart disease	3789 (28.0)	1225 (20.6)	1110 (31.2)	218 (35.6)	547 (34.4)	689 (37.5)	<.001
Hypertension	6465 (47.8)	2405 (40.5)	1794 (50.4)	340 (55.6)	869 (54.7)	1057 (57.5)	<.001
Congenital heart disease	104 (0.8)	30 (0.5)	35 (1.0)	5 (0.8)	12 (0.8)	22 (1.2)	.008
Cerebrovascular	1115 (8.2)	323 (5.4)	348 (9.8)	66 (10.8)	180 (11.3)	198 (10.8)	<.001
Stroke	732 (5.4)	228 (3.8)	247 (6.9)	33 (5.4)	105 (6.6)	119 (6.5)	<.001
Other cerebrovascular disease	532 (3.9)	130 (2.2)	157 (4.4)	40 (6.5)	94 (5.9)	111 (6.0)	<.001
Neurological/musculoskeletal	5484 (40.5)	1868 (31.5)	1575 (44.2)	302 (49.3)	774 (48.7)	965 (52.5)	<.001
Dementia	1095 (8.1)	258 (4.3)	322 (9.0)	79 (12.9)	208 (13.1)	228 (12.4)	<.001
Other neuromuscular	5110 (37.8)	1757 (29.6)	1477 (41.5)	275 (44.9)	711 (44.7)	890 (48.4)	<.001
Down syndrome	27 (0.2)	15 (0.3)	8 (0.2)	0 (0.0)	4 (0.3)	0 (0.0)	.069
Endocrine/metabolic	8838 (65.3)	3533 (59.5)	2401 (67.4)	457 (74.7)	1146 (72.1)	1301 (70.7)	<.001
Diabetes (all types)	4849 (35.8)	1940 (32.7)	1360 (38.2)	248 (40.5)	599 (37.7)	702 (38.2)	<.001
Other endocrine/metabolic disease	7772 (57.4)	3008 (50.7)	2116 (59.4)	415 (67.8)	1042 (65.5)	1191 (64.8)	<.001
Hematologic	1672 (12.4)	663 (11.2)	500 (14.0)	76 (12.4)	198 (12.5)	235 (12.8)	.081
Renal	3731 (27.6)	1133 (19.1)	1121 (31.5)	221 (36.1)	571 (35.9)	685 (37.2)	<.001
Hepatic	1546 (11.4)	603 (10.2)	428 (12.0)	72 (11.8)	213 (13.4)	230 (12.5)	<.001
Immunocompromising condition	2421 (17.9)	751 (12.7)	689 (19.3)	144 (23.5)	399 (25.1)	438 (23.8)	<.001
COVID-19 vaccination status							<.001

Characteristic	Variant-Predominant Period ^a					P Value ^b
	Overall	Delta	BA.1	BA.2	BA.4/BA.5 Post-BA.4/BA.5	
Unvaccinated	8813 (65.1)	5034 (84.8)	2324 (65.3)	220 (35.9)	610 (38.4)	625 (34.0)
Completed primary series	2913 (21.5)	865 (14.6)	990 (27.8)	195 (31.9)	412 (25.9)	451 (24.5)
Primary series + 1 booster dose (1st booster)	1318 (9.7)	35 (0.6)	243 (6.8)	182 (29.7)	413 (26.0)	445 (24.2)
Primary series + 2 booster doses (1st & 2nd booster)	388 (2.9)	0 (0.0)	4 (0.1)	15 (2.5)	151 (9.5)	218 (11.9)
Primary series + 3 booster doses (1st, 2nd, & 3rd booster)	101 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.3)	97 (5.3)
Primary series + 4 booster doses (1st, 2nd, 3rd & 4th booster)	3 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.2)
Any bivalent dose ^c	284 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	15 (0.9)	269 (14.6)
SARS-CoV-2 infection and related factors						
Historical positive test (pre-Omicron)	401 (3.0)	109 (1.8)	109 (3.1)	25 (4.1)	71 (4.5)	87 (4.7)
Historical positive test (Omicron)	426 (3.1)	0 (0.0)	66 (1.9)	51 (8.3)	138 (8.7)	171 (9.3)

Data are presented as No. (column %) unless otherwise indicated.

Abbreviations: COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; IQR, interquartile range; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SVI, Social Vulnerability Index; UMC, underlying medical condition.

^aDate ranges across sites for variant-predominant periods included: Delta: 1 June–29 December 2021; Omicron BA.1: 16 December 2021–30 March 2022; Omicron BA.2/BA.2.12.1: 17 March–29 June 2022; Omicron BA.4/BA.5: 19 June–29 October 2022; post-Omicron BA.5: 29 October 2022–29 March 2023.

^bThe Cochran-Armitage test was used for binary variables and the Jonckheere-Terpstra test was performed for continuous and ordered categorical variables with >2 groups. Categories of race and ethnicity were treated as binary (yes/no) variables with individual *P* values presented.

^cSVI was not available for 5641 (41.7%) severe encounters. Two sites contributing 2587 (19.1%) severe encounters had no SVI data available and SVI data were missing for 3054 (22.6%) of severe encounters from the remaining sites.

^dCategories of UMCs include respiratory or pulmonary, cardiovascular, cerebrovascular, neurological or musculoskeletal, endocrine or metabolic, hematologic, renal, hepatic, and immunocompromising conditions.

^eAny mRNA vaccine doses received on or after 2 September 2022 were considered to be bivalent.