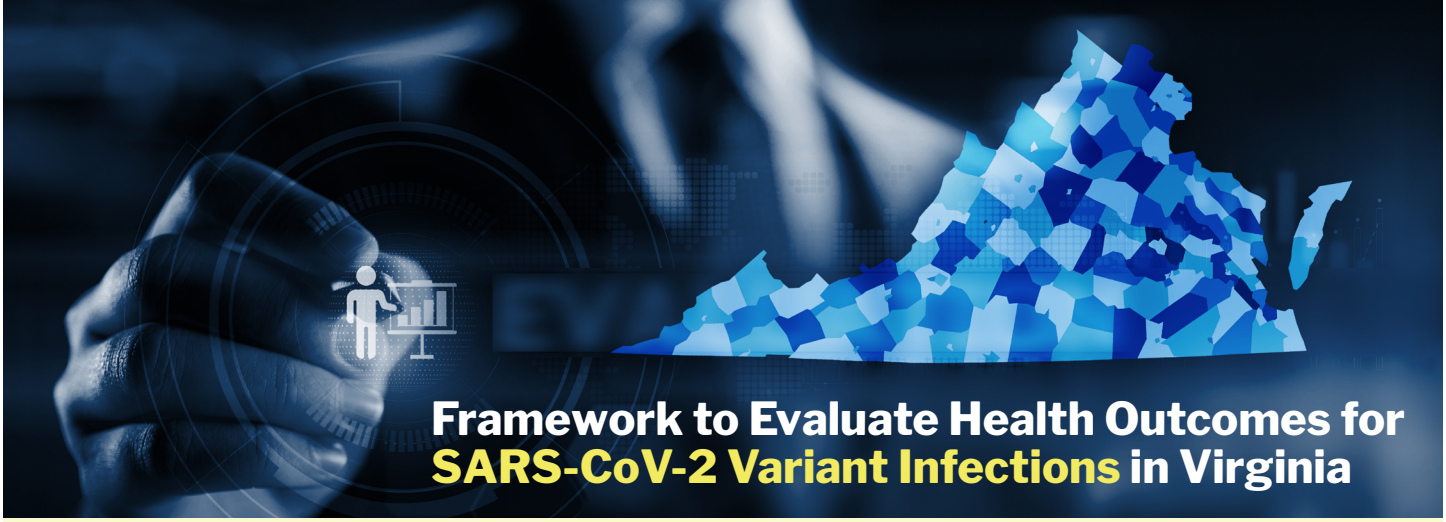

Framework to Evaluate Health Outcomes for SARS-CoV-2 Variant Infections in Virginia

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (COVID-19), is an RNA virus with a high genetic mutation rate. Genomic surveillance routinely monitors for emerging viral variants, tracks their persistence over time, and allows for epidemiological study of descendent lineages in human populations. The Virginia SARS-CoV-2 Strain Surveillance Network is led by the Division of Consolidated Laboratory Services (DCLS), which is the state's public health laboratory, and includes academic and commercial laboratory partnerships to conduct routine SARS-CoV-2 genomic surveillance. At full capacity, this Virginia laboratory network can report between 1,000-1,400 sequences per week.

In the United States, SARS-CoV-2 lineages are classified as variants being monitored (VBM), variants of interest (VOI), variants of concern (VOC), or variants of high consequence (VOHC), in order of increasing potential public health significance *(1)*. As of September 2023, the World Health Organization has designated five variants as VOC: Alpha, Beta, Gamma, Delta, and Omicron *(2)*. The Alpha (B.1.1.7) variant was first detected in Virginia in January 2021, and was predominant (>50% prevalent) through June 2021 *(2)*. This was replaced by Delta (B.1.617.2 and AY sublineages) throughout the summer and fall of 2021. The Omicron (B.1.1.529, BA sublineages) VOC was first detected in Virginia in early December 2021, and quickly outpaced its predecessor to become the predominant variant in Virginia by the end of 2021 *(2)*. Among these VOCs, severe health outcomes (i.e., hospitalization and death) have differed, with the Delta variant having been the most pathogenic to date *(3,4)*. Outcomes can also be affected by co-morbidities *(5)*, social determinants of health (SDH) *(6)*, or immunity *(7)*.

Methods

We used a retrospective cohort study design to analyze available data for Virginia persons with a COVID-19 case investigation start date in the Virginia Electronic Disease Surveillance System (VEDSS) during October 4, 2020-February 15, 2022. Analysis focused on cases with infecting viral isolate WGS results classified as Alpha (B.1.1.7), Delta (B.1.617.2 and AY lineages), Omicron (B.1.1.529 and BA lineages), or other non-dominant grouped lineages (Beta – B.1.351, Epsilon – B.1.427 & B.1.429, Eta – B.525, Iota – B.1526, Gamma – P.1, Zeta – P.2, and other unclassified lineages). Custom modules in the DCLS laboratory information management system transferred variant information to VEDSS using HL7 messaging.

Patient demographic data, variant type, and previous COVID-19 infection data were exported from VEDSS for analysis. Hospitalization data was collected from voluntary interviews conducted by local public health department personnel and stored in VEDSS. Mortality data reflect patients where COVID-19 was the underlying cause of death as listed on a death certificate. VDH's Office of Health Equity provided matched Health Opportunity Index (HOI) data (8), an aggregated measure of 13 social determinants of health indicators on a continuous scale from 0-1, with higher numbers representing greater opportunities for health. Dates of COVID-19 vaccination(s) and vaccine manufacturer data were matched from the

Virginia Immunization Information System (VIIS), Virginia's statewide vaccination registry.

We used adjusted multivariable logistic regression to test whether hospitalization and death occurred uniformly across predominant variants, using persons infected with non-dominant lineages as the baseline comparative population. Age was included as a continuous variable with a cubic spline (5 knots), sex as a binary variable, and combined race and ethnicity as a factored variable were demographic covariates[1]. Investigation start month was included to control for time as available countermeasures varied during the pandemic, which might have affected patient outcomes. Reinfection status, as a binary variable representing whether a person was identified as a previously confirmed COVID-19 case from 90 to 180 days before their sequenced variant infection, controlled for potential immunity from a previous SARS-CoV-2 infection (9). Evidence of prior vaccination (with at least one dose of an FDA-approved COVID-19 vaccine) was included as a binary variable to control for vaccine-induced immunologic protection. Finally, HOI quintiles were included as an ordered categorical measure of social determinants of health.

An adjusted multivariable regression model was used to analyze vaccine breakthrough infection by variant type with age (cubic spline, 5 knots) and calendar month of investigation start date as covariates. Persons who had a previous positive COVID-19 nucleic acid amplification test recorded in VEDSS between 14 and 90 days preceding the sequenced positive test result were excluded from vaccine breakthrough analyses, as the qualifying test could be consistent with a person persistently testing positive after acute infection (10). Persons with incomplete vaccination, as determined by evidence of not completing their primary vaccination series as recorded in VIIS, were also excluded. We performed all analyses in R Statistical Software (version 4.2.2; R Core Team 2021).

Results

We identified 43,964 patients with COVID-19 WGS variant results during October 4, 2020–February 15, 2022 (Table 1). The median age of persons in the cohort was 37 years (IQR = 34), with reported current sex as 52.6% women, 47.3% men, and <0.1% unknown. Of the 37,546 persons with reported ethnicity, 3,510 (9.3%) identified as Hispanic. Among 37,890 persons with recorded race data, 26,980 (71.2%) were White, 7,950 (21.0%) were Black, 1,572 (4.1%) were Asian, 1,203 (3.2%) were two or more races, 121 (0.3%) were American Indian or Alaska Native, and 64 (0.2%) were Native Hawaiian or Other Pacific Islander.

WGS variant results revealed 26,130 (59.4%) infections were Delta, 11,761 (26.8%) were Omicron, 3,042 (6.9%) were Alpha, and 3,031 (6.9%) were non-dominant variants (Figure 1). Of the 26,130 persons with Delta infections, 1,276 (4.9%) were hospitalized, 641 (2.5%) died, and 4,449 (17.0%) represented a vaccine breakthrough infection. Of the 3,042 persons with Alpha infections, 178 (5.9%) were hospitalized, 42 (1.4%) died, and 148 (4.9%) represented a vaccine breakthrough infection. Of the 11,761 persons with Omicron infections, 252 (2.1%) were hospitalized, 128 (1.1%) died, and 4,557 (38.7%) had a vaccine breakthrough infection. Of the 3,031 persons with non-dominant infections, 141 (4.7%) were hospitalized, 57 (1.9%) died, and 404 (13.3%) represented a vaccine breakthrough infection (Figure 1).

Hospitalization

A total of 1,847 (4.2%) persons were hospitalized from COVID-19 in this cohort. The median age was 65 years (IQR = 25), with reported current sex as 50.1% women, 49.8% men, and 0.1% unknown.

In a multivariable regression with demographic, time, reinfection, vaccination, and SDH covariates, the odds of hospitalization increased by 76% (adjusted odds ratio [aOR] 1.76, CI 1.35–2.33) with a Delta infection and decreased by 34% (aOR 0.66, CI 0.49–0.91) with an Omicron infection, as compared to non-dominant lineage infections (Table 2). Persons with Alpha infections did not have statistically significantly different odds of hospitalization. Receiving at least one COVID-19 vaccine prior to a person's COVID-19 investigation date was protective against hospitalization (aOR 0.51, CI 0.45–0.57).

[1]Tiered categories included: Asian, Native Hawaiian, or Other Pacific Islander, Black, White, Hispanic (and any race), race not provided or unknown, other race, multiple races.

Death

A total of 868 (2.0%) persons in this cohort died from COVID-19. The median age was 71 years (IQR = 21), with reported current sex as 55.3% men and 44.7% women.

Using multivariable regression with demographic, time, reinfection, vaccination, and HOI covariates, the odds of dying increased by 156% with a Delta infection (aOR 2.56, CI 1.70–3.96) when compared to non-dominant lineage infections (Table 2).

Persons with Alpha or Omicron infections did not have statistically significantly different odds of death. Receiving at least one COVID-19 vaccine prior to a person's COVID-19 investigation date was protective against death (aOR 0.41, CI 0.39-0.48)

(703.8/100,000), while 2022 life expectancy, although improved from 2021, was still lower than that of 2019.

Vaccine Breakthrough

We identified 9,558 persons with SARS-CoV-2 vaccine breakthrough infections. The average time from completing the primary COVID-19 vaccination series to COVID-19 investigation date was 211 days (SD = 85.9).

In an adjusted multivariable regression with age and calendar month as covariates, the odds of vaccine breakthrough were 41% lower for Alpha infections (aOR 0.59, CI 0.46–0.76), 24% higher for Delta infections (aOR 1.24, CI 1.09–1.42), and 205% higher for Omicron infections (aOR 3.05, CI 2.69–3.46) when compared to non-dominant lineages.

Discussion

We demonstrated increased odds of hospitalization and mortality among persons with Delta infections, which is supported in similar studies *(11-14)*. Omicron had reduced odds of hospitalization and mortality, aligning with other findings of decreased disease severity *(15,16)*. Whether these differences are due to inherent differences in viral pathogenicity between variants and/or due to better population immunity from vaccination and natural infection during the Omicron wave cannot be determined from this study *(17)*.

Odds of vaccine breakthrough increased with Delta and further increased with Omicron as expected *(18,15)*. Greater rates of vaccine breakthrough infection in subsequent variant waves could be at least partially due to increased population vaccination rates. Mutations in the Delta and Omicron viral spike proteins compared to the spike protein used in the original COVID-19 vaccines contributed to the observed increases in odds of vaccine breakthrough infection is also a plausible explanation *(18)*. We demonstrated average time to breakthrough of approximately seven months from primary vaccine series completion, consistent with a meta-analysis finding declining vaccine protection around this time *(19)*. Although breakthrough infections occurred frequently, vaccination continued to provide protection against severe health outcomes, as evident in our study findings.

Our study has multiple limitations. First, while certain underlying medical conditions are associated with more severe COVID-19 health outcomes, insufficient data prevented including these data as model covariates. Second, genomic surveillance data is not intended to be representative of the general population. During the study period, 1,048,575 confirmed and probable cases of COVID-19 were reported to VEDSS; however, our cohort reflects only 4.2% of these cases. Samples were prioritized for WGS testing during the study period in multiple circumstances as follows: (1) cases in persons with recent international travel to destinations with emerging variants; (2) illnesses that were more severe than expected; (3) cases of potential reinfection or vaccine breakthrough; (4) samples collected during recognized outbreaks; and (5) samples with unusual diagnostic results. Additionally, not all positive SARS-CoV-2 samples were available to be sequenced because of sample quality, logistical concerns, or financial limitations.

This study represents the culmination of work performed by multiple agencies and departments within the Virginia state government. VDH and DCLS have a close working relationship, as DCLS serves as the public health testing laboratory for

Virginia. The siloing of WGS and health information between the two organizations during the COVID-19 pandemic prompted efforts to improve data transfer, integration, and utilization for better data synthesis, decision making, and surveillance; it was recognized that the ability to track and characterize the COVID-19 health-outcomes data and correlate it with the sample sequencing data would lead to better insights into the disease dynamics of the SARS-CoV-2 virus in the Commonwealth. The improved correlation of health records with lineage typing information allowed for the building out of variant data dashboards for public viewing *(20)*, and studies into the trends and the public health impacts of an evolving pandemic pathogen. This newly placed infrastructure to synthesize SARS-CoV-2 health outcomes and sequencing information has highlighted the need to expand data usage agreements between VDH and DCLS for future genomic surveillance and outbreak response efforts for SARS-CoV-2 and other pathogens. This continued coordination and analytical framework has direct implications for future SARS-CoV-2 variant public health analysis, as well as adverse health outcome and vaccine breakthrough comparisons between other emerging or re-emerging diseases.

References

Centers for Disease Control and Prevention. SARS-CoV-2 Variant Classifications and Definitions. Published April 26, 2022. https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-classifications.html. Accessed 20 March 2023.

World Health Organization: Tracking SARS-CoV-2 variants. Accessed July 31, 2023. https://www.who.int/en/activities/tracking-SARS-CoV-2-variants.

Miyashita K, Hozumi H, Furuhashi K, et al. Changes in the characteristics and outcomes of COVID-19 patients from the early pandemic to the delta variant epidemic: A nationwide population-based study. *Emerging Microbes & Infections.* 2022;12(1). https://doi:10.1080/22221751.2022.2155250

Adjei S, Hong K, Molinari NM, et al. Mortality Risk Among Patients Hospitalized Primarily for COVID-19 During the Omicron and Delta Variant Pandemic Periods — United States, April 2020–June 2022. *MMWR Morb Mortal Wkly Rep* 2022;71:1182–1189. http://dx.doi.org/10.15585/mmwr.mm7137a4

Centers for Disease Control and Prevention. Underlying Medical Conditions Associated with Higher Risk for Severe COVID-19: Information for Healthcare Professionals. Updated February 9, 2023. https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html Accessed 3/29/2023.

Abrams EM, Szefler SJ. COVID-19 and the impact of social determinants of health. *Lancet Respir Med*. 2020 Jul;8(7):659-661. https://doi:10.1016/S2213-2600(20)30234-4. Epub 2020 May 18. PMID: 32437646; PMCID: PMC7234789.

Mensah AA, Lacy J, Stowe J, et al. Disease severity during SARS-COV-2 reinfection: a nationwide study. *J Infect*. 2022;84(4):542-550. https://doi:10.1016/j.jinf.2022.01.012

Virginia Department of Health Office Health Equity. Virginia Health Opportunity Index. https://apps.vdh.virginia.gov/omhhe/hoi/. Accessed 2/9/2023.

European Commission. EU Digital COVID Certificate. 2022. Accessed August 2, 2023. https://ec.europa.eu/info/live-work-travel-eu/coronavirus-response/safe-covid-19-vaccines-europeans/eu-digital-covid-certificate_en

Rosenberg ES, Holtgrave DR, Dorabawila V, et al. New COVID-19 Cases and Hospitalizations Among Adults, by Vaccination Status — New York, May 3–July 25, 2021. *MMWR Morb Mortal Wkly Rep* 2021;70:1306–1311. doi: http://dx.doi.org/10.15585/mmwr.mm7037a7

Fisman DN, Tuite AR. Evaluation of the relative virulence of novel SARS-COV-2 variants: A retrospective cohort study in Ontario, Canada. *Canadian Medical Association Journal.* 2021;193(42). https://doi:10.1503/cmaj.211248

Bast E, Tang F, Dahn J, Palacio A. Increased risk of hospitalisation and death with the Delta variant in the USA. *The Lancet Infectious Diseases.* 2021;21(12):1629-1630. https://doi:10.1016/s1473-3099(21)00685-x

Adjei S, Hong K, Molinari NM, et al. Mortality

Risk Among Patients Hospitalized Primarily for COVID-19 During the Omicron and Delta Variant Pandemic Periods — United States, April 2020–June 2022. *MMWR Morb Mortal Wkly Rep* 2022;71:1182–1189. DOI: http://dx.doi.org/10.15585/mmwr.mm7137a4

Sheikh A, McMenamin J, Taylor B, Robertson C. SARS-COV-2 delta voc in Scotland: Demographics, risk of hospital admission, and Vaccine Effectiveness. *The Lancet*. 2021. https://doi.org/10.1016/S0140-6736(21)01358-1

Christensen PA, Olsen RJ, Long SW, et al. Signals of Significantly Increased Vaccine Breakthrough, Decreased Hospitalization Rates, and Less Severe Disease in Patients with Coronavirus Disease 2019 Caused by the Omicron Variant of Severe Acute Respiratory Syndrome Coronavirus 2 in Houston, Texas. *Am J Pathol*. 2022;192(4):642-652. https://doi:10.1016/j.ajpath.2022.01.007

Aiello TF, Puerta-Alcalde P, Chumbita M, et al. Infection with the Omicron variant of SARS-CoV-2 is associated with less severe disease in hospitalized patients with COVID-19. *J Infect*. 2022;85(5):e152-e154. https://doi:10.1016/j.jinf.2022.07.029

Carabelli, A.M., Peacock, T.P., Thorne, L.G. et al. SARS-CoV-2 variant biology: immune escape, transmission and fitness. *Nat Rev Microbiol* 21, 162–177 (2023). https://doi.org/10.1038/s41579-022-00841-7

Zhang M, Liang Y, Yu D, et al. A systematic review of Vaccine Breakthrough Infections by SARS-CoV-2 Delta Variant. *Int J Biol Sci*. 2022;18(2):889-900. Published 2022 Jan 1. https://doi:10.7150/ijbs.68973

Feikin DR, Higdon MM, Abu-Raddad LJ, et al. Duration of effectiveness of vaccines against SARS-CoV-2 infection and COVID-19 disease: results of a systematic review and meta-regression [published correction appears in *Lancet*. 2022 Apr 4;:] [published correction appears in *Lancet*. 2023 Feb 25;401(10377):644]. *Lancet*. 2022;399(10328):924-944. https://doi:10.1016/S0140-6736(22)00152-0

Virginia Department of Health. Variants Dashboard. https://www.vdh.virginia.gov/coronavirus/see-the-numbers/covid-19-in-virginia/#variants. Accessed 6 June 2023.

Acknowledgments

We would like to thank Eleanor Field, Brandy Darby, Logan Fink, Jenny Crain, Rachael St. Jacques, Lauren Turner, Jonathan Falk, Rexford Anson-Dwamena, and Samuel Masse for their tireless efforts in collecting and preparing these data. We would also like to thank Elena Diskin and Heather Harmon-Sloan for their assistance with providing total COVID-19 data in Virginia. We would like to thank Tommy Xia for assistance with Health Opportunity Index data.

Statement of Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Research ethics, patient consent, and statement of ethics review

This study was approved by the Virginia Department of Health Institutional Review Board (#50270).

Table 1: Characteristics and SARS-CoV-2 variant whole genome sequencing results for a COVID-19 cohort (N = 43,964) in Virginia during October 4, 2020-February 15, 2022.

Characteristic	n (%*)
Current Sex	
Women	23,110 (52.6)
Men	20,791 (47.4)
Missing current sex	63
Age group	
0-9	4,276 (9.7)
10-19	6,016 (13.7)
20-29	7,453 (17.0)
30-39	7,013 (16.0)
40-49	5,883 (13.4)
50-59	5,391 (12.3)
60-69	4,113 (9.4)
70-79	2,386 (5.4)
80+	1,429 (3.3)
Missing age	4
Ethnicity	
Hispanic	3,510 (9.3)
Non-Hispanic	34,046 (90.7)
Missing ethnicity	6,418
Race	
Asian or Pacific Islander	121 (0.3)
Black	7,950 (19.0)
American Indian or Alaska Native	651 (1.6)
White	26,980 (64.4)
Other	3,331 (8.0)
Two or more	1,203 (2.9)
Missing race	2,092
Variant type	
Alpha	3,031 (7.0)
Delta	26,130 (59.0)
Omicron	11,761 (27.0)
Other non-dominant	3,042 (7.0)

Calculated percentages do not include missing values.

Table 2: Adjusted odds ratios (aOR) for severe health outcomes[1] and for vaccine breakthrough[2] by SARS-CoV-2 variant type confirmed by whole genome sequencing, for a COVID-19 cohort in Virginia during October 4, 2020-February 15, 2022.

	Hospitalization aOR (95% CI [3]) n = 1,847	Mortality aOR (95% CI) n = 868	Vaccine breakthrough aOR (CI) n = 9,558
Alpha	1.05 (0.76–1.44)	0.91 (0.52–1.59)	0.59 (0.46–0.76)*
Delta	1.76 (1.35–2.33)*	2.56 (1.70–3.96)*	1.09 (1.09–1.42)*
Omicron	0.67 (0.49–0.91)*	0.73 (0.47–1.16)	3.05 (2.69–3.46)*

*Statistically significant at $p < 0.05$

[1]Covariates included age, current sex, race and ethnicity, COVID-19 reinfection status, month of COVID-19 investigation date, history of prior vaccination, and Health Opportunity Index category.

[2]Covariates included age and calendar month of COVID-19 investigation date.

[3]Confidence Interval

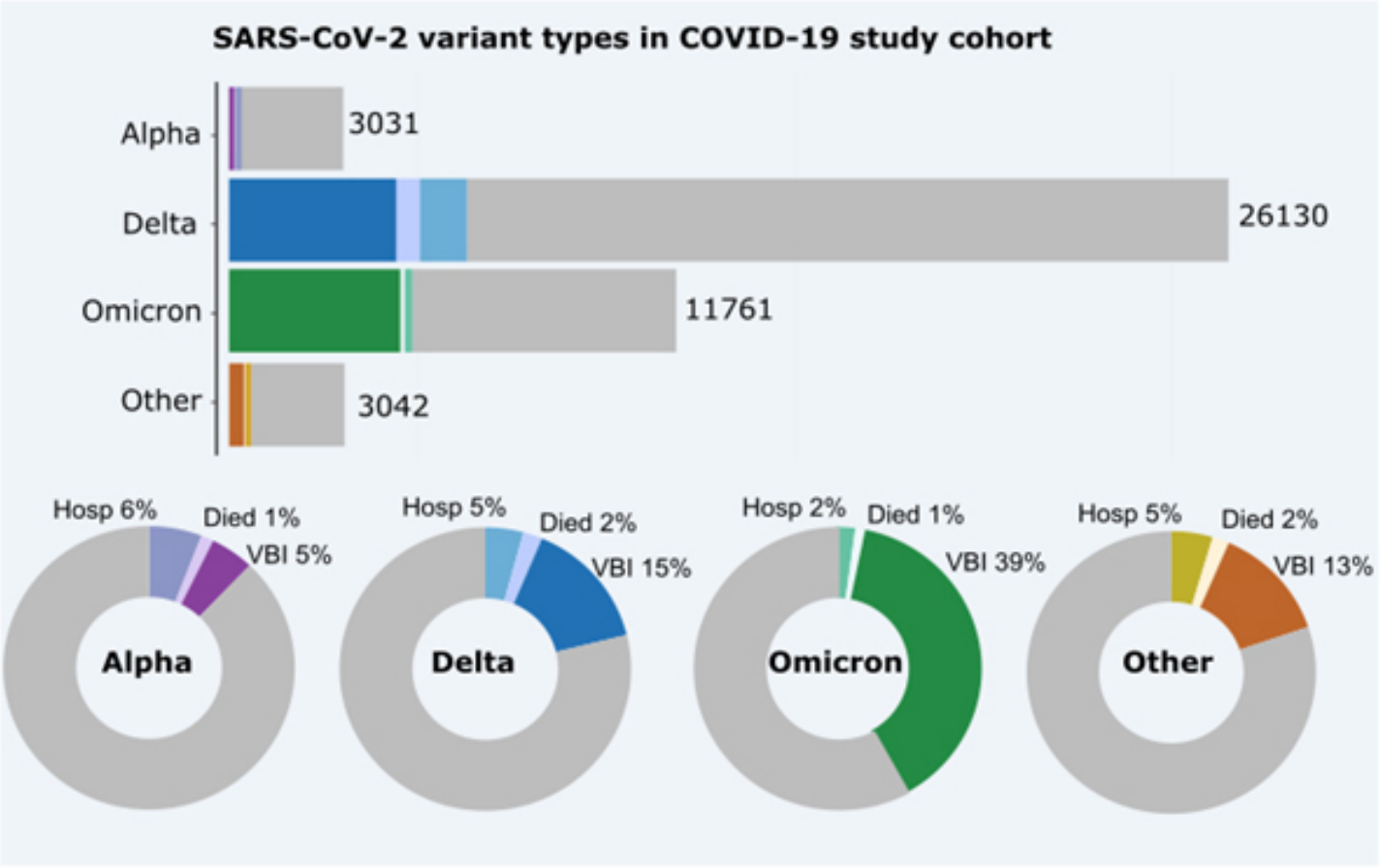

Figure 1: Whole genome sequenced SARS-CoV-2 variant type counts for COVID-19 case patients in the study cohort (N = 43,964) during October 4, 2020–February 15, 2022. Coloration within bars corresponds with health outcomes designated below. Pie charts represent the rounded percentages of patients who were hospitalized (N = 1,847), died (N = 868), or had a vaccine breakthrough infection (VBI) (N = 9,558) by variant type. The representative graphs above included events collectively and thus contain duplicates; 383 people were hospitalized and died, 57 people were hospitalized, died, and had VBI, 50 people died and had VBI, and 163 people were hospitalized and had VBI.