

# Baseline COVID-19 Severity Metrics, US

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Critchley, Lacey; Lewis, Bryan; Venkatramanan, Srin; Warren, Andrew

## Introduction

There is a need in the scientific literature for more studies analyzing the relationship between COVID-19 strain and associated severity and how this relationship has changed over time given the evolution of strains and sublineages as well as the changing landscape of immunity.

This analysis uses data from the National COVID Cohort Collaborative (N3C) to calculate baseline severity metrics for the US per 8 distinct epochs of time during the COVID pandemic:

1. Wildtype: 2020-03-01 to 2020-09-01
2. FallWinter2020: 2020-09-01 to 2021-03-15
3. Alpha/Vax period: 2021-03-15 to 2021-07-01
4. Delta B.1.617.2 period: 2021-07-01 to 2021-12-01
5. BA.1/BA.2.75 period: 2021-12-01 to 2022-03-15
6. BA.4/5 period: 2022-03-15 to 2022-10-31
7. XBB/BQ.1.1 period: 2022-10-31 to 2023-03-15
8. POST-XBB period: 2023-03-15 to 2023-07-31

## Data Collection

### *National COVID Cohort Collaborative (N3C)*

Data was collected using the National COVID Cohort Collaborative (N3C), under project RP-9A216C - Assessing Severity of Disease based on Immune History and Variant. The N3C offers one of the largest collections of secure, deidentified clinical data in the United States for COVID-19 research. The N3C is a partnership among the National Center for Advancing Translational Science (NCATS)-supported Clinical and Translational Science Awards (CTSA) Program hubs, the National Center for Data to Health (CD2H), and the National Institute of General Medical Sciences (NIGMS)-supported Institutional Development Award Networks for Clinical and Translational Research (IDeA-CTR), with overall stewardship by NCATS. It is a centralized, harmonized, high-granularity electronic health record (EHR) repository that is the largest, most representative COVID-19 cohort to date (but it is important to note that N3C is not considered nationally representative, so proceed with caution when interpreting results). It contains three tiers of data – synthetic, limited data set (LDS; dates of service, zip code), and fully de-identified. Once per week, N3C pulls COVID-positive patient data and twice as many demographically matched controls (as of February 2024: 8.6M COVID+, 22M patients, 31.8B rows) from 83 sites.

### *Defining Severity*

Severity of infection in N3C was measured with records of COVID-associated hospitalization, which was defined as an inpatient visit with a start date 1 day prior to 16 days after the COVID-19 index date with a COVID diagnosis code used during the visit. A COVID-associated emergency department (ED) visit was defined as an ED visit with a start date 1 day prior to 16 days after the COVID-19 index date. These thresholds were intended to capture hospitalizations and ED visits that are related to COVID. Severity of infection is assessed with hospitalization metrics associated with those hospital or ED visits. Five levels of severity are considered:

- 1) Mild infection that does not require an ED visit or hospitalization
- 2) Mild infection that requires an ED visit
- 3) Moderate infection that requires hospitalization
- 4) Severe infection that requires hospitalization and use of extracorporeal membrane oxygenation (ECMO), invasive mechanical ventilation (IMV), or vasopressors
- 5) Death within 60 days after initial infection

### Results

In late 2023, a dataset of 7,804,320 COVID infections, 128 variables was created (locked to release version 130, 2023-6-29 with data between January 1, 2018 and July 31, 2023), including 59,107 unique patient rows with viral strain data (WHO lineages; 59,094 PANGO lineages; 34,428 PANGO sublineages). The majority of the strain-linked patients were confirmed Delta (n=27,242), Omicron (n=16,062), and Alpha (n=11,401) lineages. All results shared have been approved for N3C export (per DRR-DCDA226).

### *Demographics of N3C dataset*

The majority of those included in the dataset were female (55.65%). The mean age was 42.3 years (SD 22.4 years). The majority were White (65.60%), followed by Black (13.31%) or Asian (2.85%). During the entire time period, the majority of patients (82.18%) included in the dataset had not had a COVID vaccine before their first infection (with the caveat that this summary data includes the time before vaccination was available). The average length of hospitalization was 0.4 days (SD 3.3 days). Thirty-eight comorbid conditions with diagnosis “before or day of COVID” were available as well.

Table 1. US dataset demographics

Characteristic	Number or Mean (Standard Deviation)	Percentage of full dataset (Total N= 7,804,320)
Sex		
Male	3,452,562	44.24%

Female	4,343,168	55.65%
Age at COVID	42.3 (SD 22.4)	
Race		
White	5,119,715	65.60%
Black	1,038,867	13.31%
Asian	222,518	2.85%
American Indian/Alaskan Native	37,034	0.47%
Native Hawaiian or Other Pacific Islander	24,039	0.31%
Hispanic or Latino	77	0.00%
Other	257,804	3.30%
Unknown	1,104,266	14.15%
Number of COVID vaccine doses before day of COVID		
0	6,413,527	82.18%
1	235,403	3.02%
2	680,311	8.72%
3	384,404	4.93%
4	90,675	1.16%
Number of COVID vaccine doses post COVID		
0	6,472,453	82.93%
1	461,547	5.91%
2	518,144	6.64%
3	276,706	3.55%
4	75,470	0.97%
Long COVID diagnosis post COVID	64,066	0.82%
Had at least one reinfection post COVID indicator	347,300	4.45%
COVID hospitalization length of stay	0.4 (SD 3.3)	
COVID patient death indicator	185,028	2.37%
Severity		
Mild – No ED or Hospitalization around COVID index	6,770,663	86.76%
Mild – ED around COVID index	563,399	7.22%
Moderate – Hospitalization around COVID index	357,200	4.58%
Severe – ECMO or IMV in Hospitalization around COVID index	18,015	0.23%
Death within 60 days after COVID index	95,043	1.22%
Has Pango lineage	59,094	0.76%
Has Pango sublineage	34,428	0.44%
Has WHO lineage	59,107	0.76%
Delta	27,242	0.35%
Omicron	16,062	0.21%

Alpha	11,401	0.15%
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*Severity outcomes*

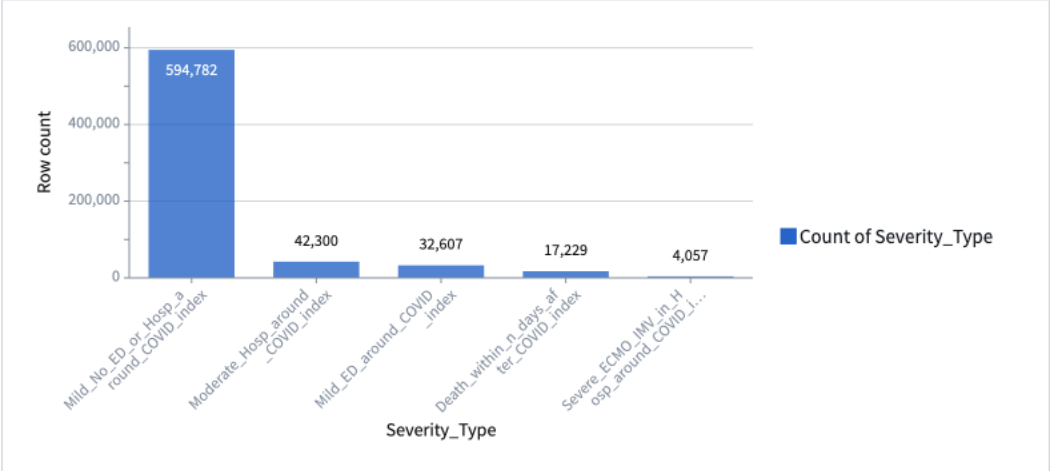
Most confirmed cases in our dataset of 7,804,320 between December 2019 and July 2023 had mild outcomes; 13.24% (n=1,033,657) of cases were hospitalized.

**Wildtype: 2020-03-01 to 2020-09-01**

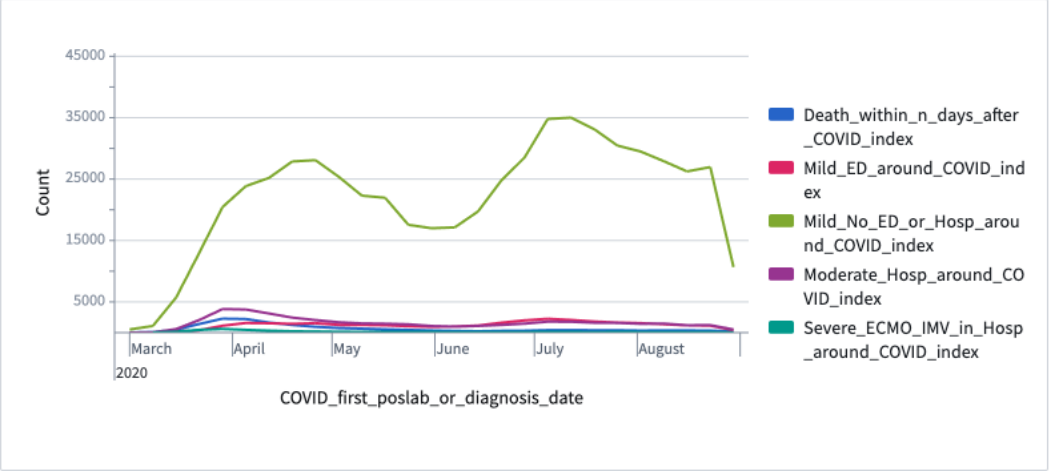
US

690,975 COVID-positive infections during the inferred 'Wildtype' epoch (2020-03-01 to 2020-09-01) were captured in our dataset. Of which 594,782 (86.08%) were mild and did not require an ED visit or hospitalization; 32,607 (4.72%) were considered mild with an ED visit; 42,300 (6.12%) were considered moderate and required hospitalization; 4,057 (0.59%) were considered severe, requiring ECMO/IMV; and 17,229 (2.49%) died within 60 days of their infection.

US Severity Counts, Wildtype



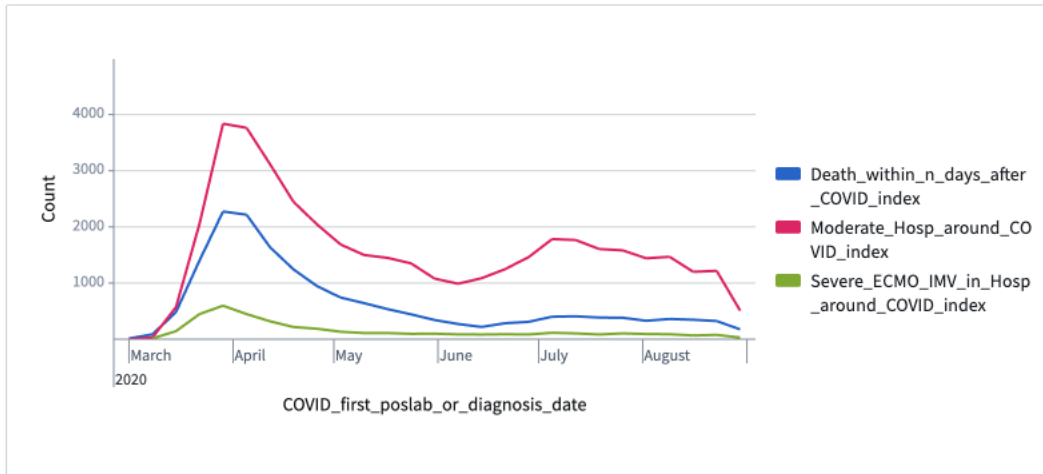
US Severity Counts Over Time, Wildtype



Of the 63,586 infections that required hospitalization, 66.52% of infections (n=42,300) were considered moderate; 6.38% (n=4,057) severe; and 27.10% (n=17,229) died within 60 days. The

mean length of hospitalization during this inferred epoch was 8.58 days; this increased to 11.17 days for “severe” infections.

US Hospitalized Severity Counts Over Time, Wildtype

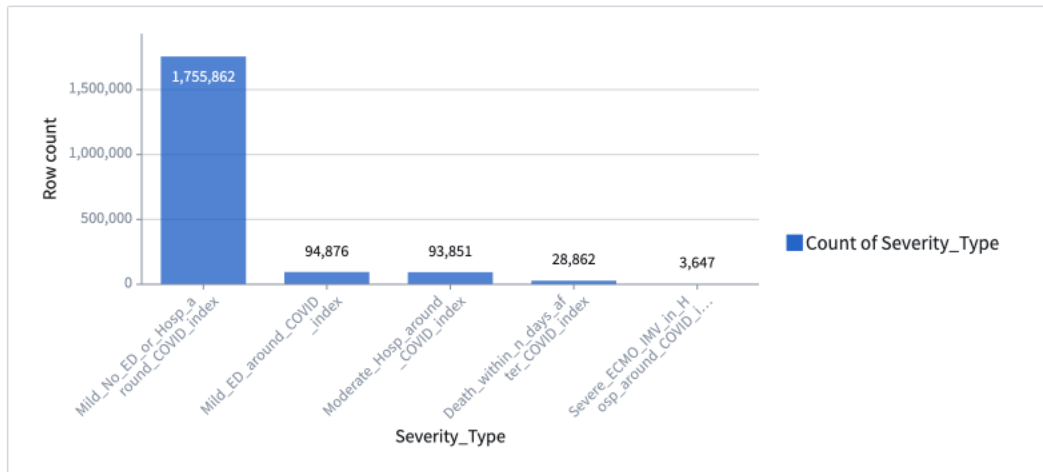


**FallWinter2020: 2020-09-01 to 2021-03-15**

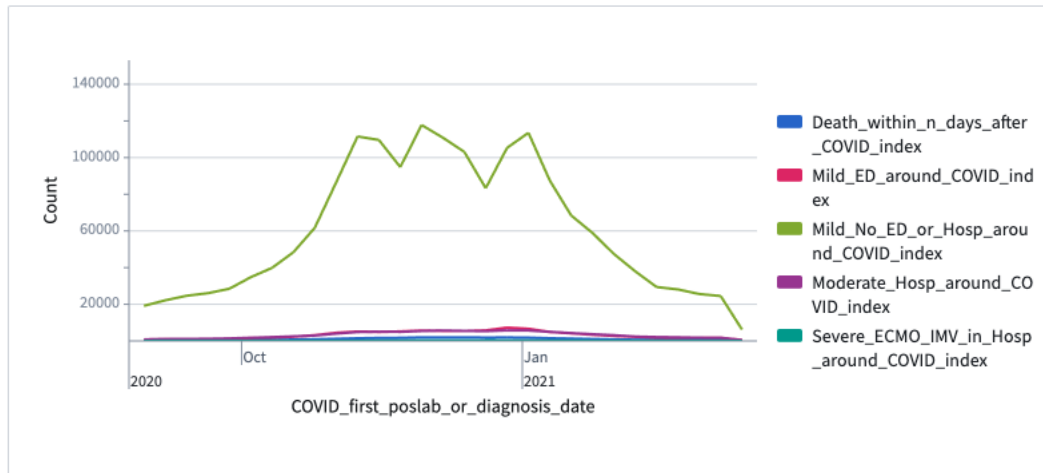
US

1,977,098 COVID-positive infections during the inferred ‘Fall Winter 2020’ epoch (2020-09-01 to 2021-03-15) were captured in our dataset. Of which 1,755,862 (88.81%) were mild and did not require an ED visit or hospitalization; 94,876 (4.80%) were considered mild with an ED visit; 93,851 (4.75%) were considered moderate and required hospitalization; 3,647 (0.18%) were considered severe, requiring ECMO; and 28,862 (1.46%) died within 60 days of their infection.

US Severity Counts, FallWinter2020

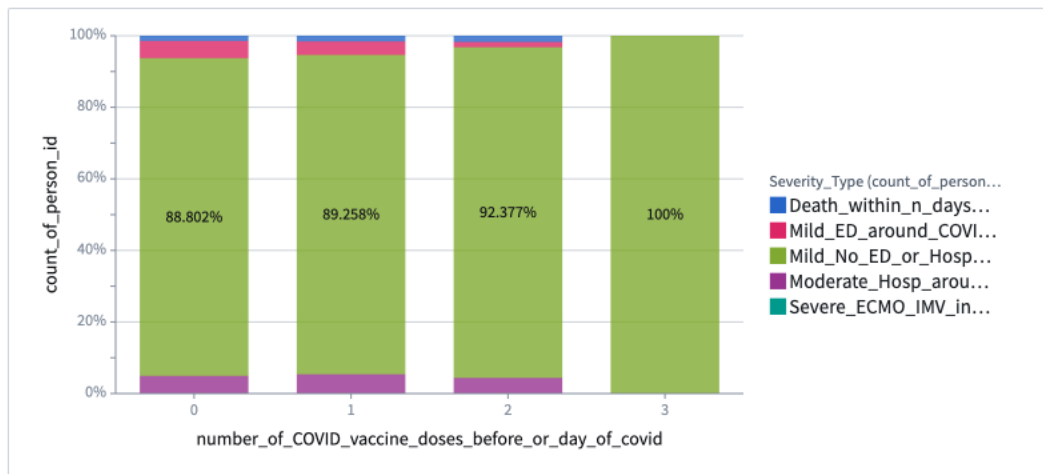


US Severity Counts Over Time, FallWinter2020



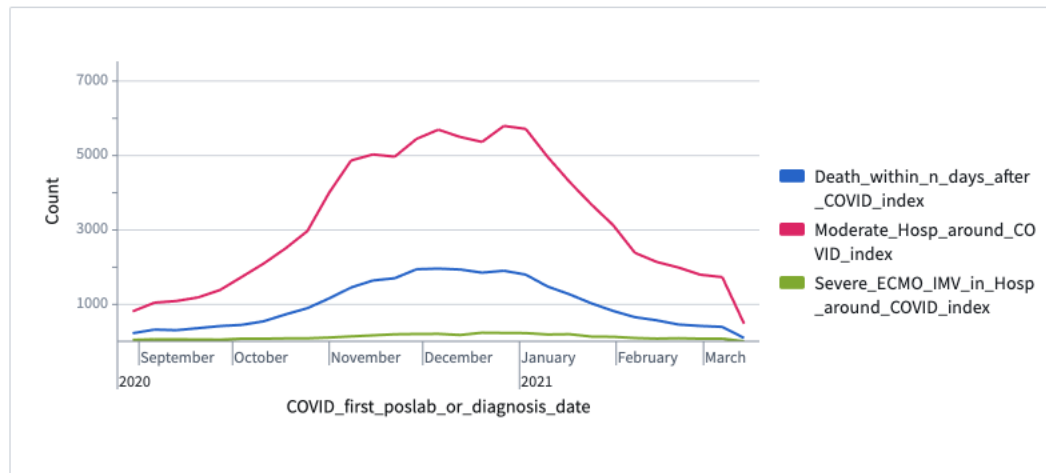
Taking into account COVID vaccination status, most infections were still mild, not requiring an ED visit or hospitalization, regardless of vaccination status or count (88.80% for no vaccination; 89.26% for 1 vaccine dose; 92.38% for 2 vaccine doses; and 100% for 3 vaccine doses). For mild infections requiring an ED visit, 4.81% had no vaccination; 3.77% had 1 vaccine dose; 1.49% had 2 vaccines doses. For moderate infections requiring hospitalization, 4.74% had no vaccination; 5.26% had 1 vaccine dose; 4.28% had two vaccine doses. For severe infections requiring ECMO/IMV, 0.19% had no vaccination; 0.12% had 1 vaccine dose; and another 0.12% had 2 vaccine doses. For infections resulting in death, 1.46% had no vaccination; 1.59% had 1 vaccine dose; 1.73% had 2 vaccine doses. Across categories (excluding death), a clear dose-response relationship is observed—the more vaccine doses a patient had, the milder their infection.

US Severity Type Percentage by Vaccination Count, FallWinter 2020



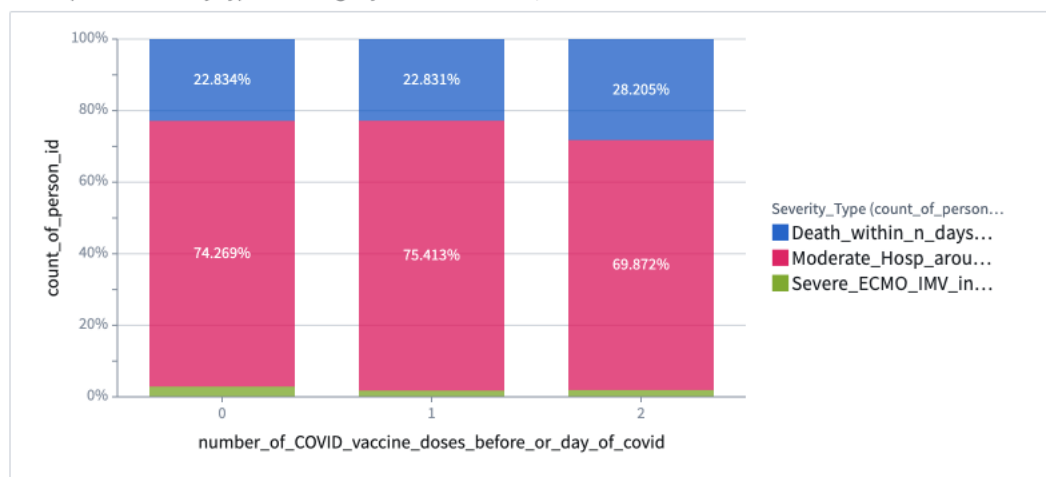
Considering only those who were hospitalized during the 'Fall Winter 2020' epoch (126,360 infections), 72.47% of infections (n= n=93,851) were considered moderate; 2.89% (n=3,647) severe; and 22.84% (n=28,862) died within 60 days. The mean length of hospitalization during this inferred epoch was 6.96 days; this increased to 8.47 days for "severe" infections.

US Hospitalized Severity Counts Over Time, FallWinter2020



Taking into account COVID vaccination status for those hospitalized, the majority of infections were considered moderate regardless of vaccination status (74.27% for no vaccination; 75.41% for 1 vaccine dose; and 69.87% for 2 vaccine doses). For those hospitalized with severe outcomes, 2.90% had no vaccination; 1.76% had 1 vaccine dose; and 1.92% had 2 vaccine doses. For hospitalized infections that resulted in death, 22.83% had no vaccination; another 22.83% had 1 vaccine dose; and 28.21% had 2 vaccine doses. Notably, no one with 3 vaccine doses at this time was hospitalized in the dataset.

US Hospitalized Severity Type Percentage by Vaccination Count, FallWinter 2020

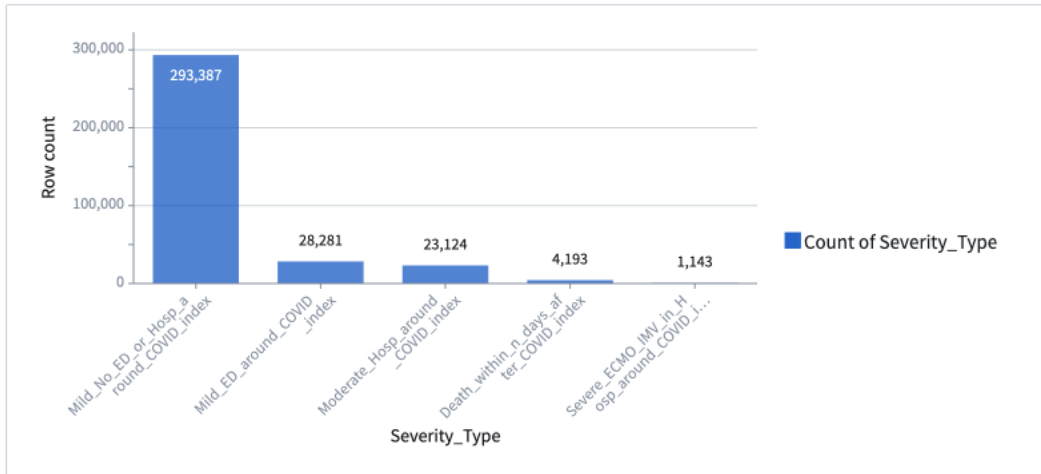


**Alpha/Vax period: 2021-03-15 to 2021-07-01**

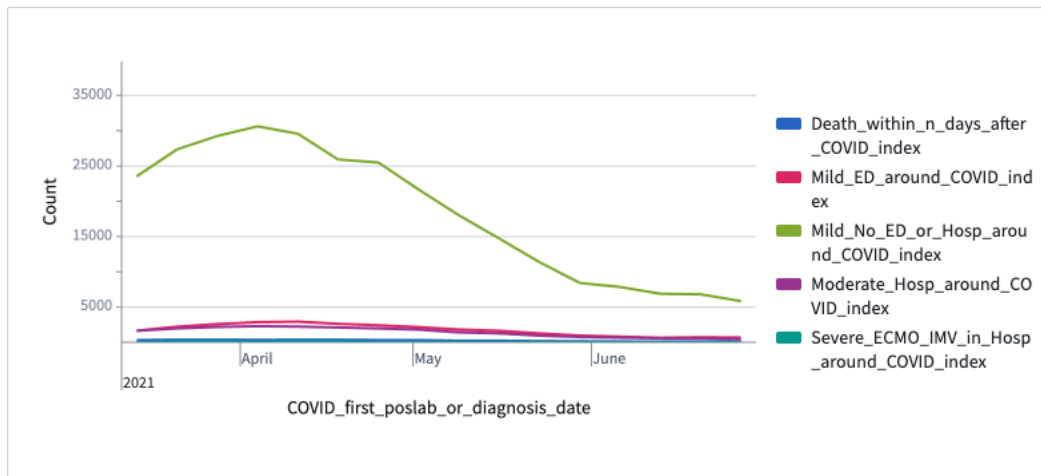
US

350,128 COVID-positive infections during the inferred 'Alpha/Vax' epoch (2021-03-15 to 2021-07-01) were captured in our dataset. Of which 293,387 (83.79%) were mild and did not require an ED visit or hospitalization; 28,281 (8.08%) were considered mild with an ED visit; 23,124 (6.60%) were considered moderate and required hospitalization; 1,143 (0.33%) were considered severe, requiring ECMO/IMV; and 4,193 (1.20%) died within 60 days of their infection.

US Severity Counts, Alpha



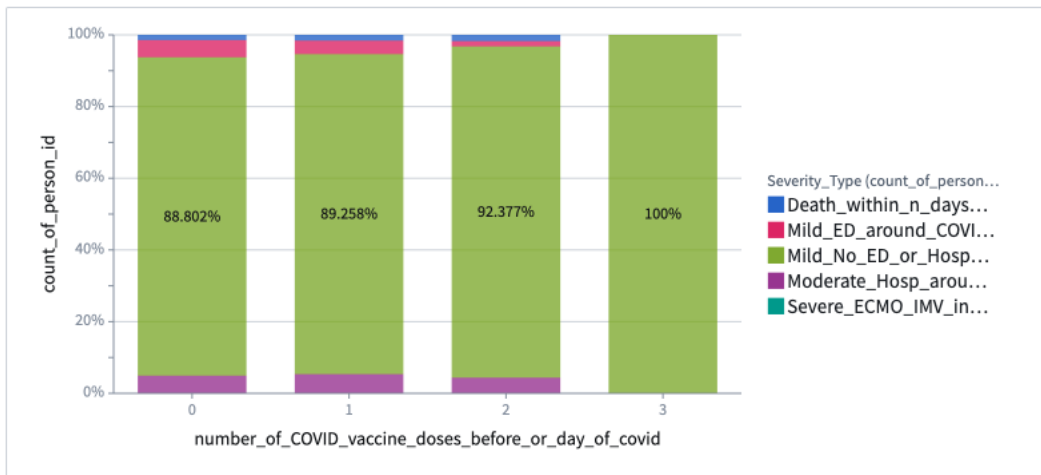
US Severity Counts Over Time, Alpha



Taking into account COVID vaccination status, most infections were still mild, not requiring an ED visit or hospitalization, regardless of vaccination status or count (83.40% for no vaccination; 88.16% for 1 vaccine dose; 89.80% for 2 vaccine doses; 93.33% for 3 vaccine doses; and 90.91% for 4 vaccine doses). For mild infections requiring an ED visit, 8.37% had no vaccination; 5.46% had 1 vaccine dose; 2.96% had 2 vaccine doses; and 2.22% had 3 vaccine doses. For moderate infections requiring hospitalization, 6.69% had no vaccination; 5.41% had 1 vaccine dose; 5.75% had 2 vaccine doses; 2.22% had 3 vaccine doses; and 9.09% had 4 vaccine doses. For severe infections requiring ECMO/IMV, 0.33% had no vaccination; 0.25% had 1 vaccine dose; and 0.23% had 2 vaccines. For infections resulting in death, 1.22% had no vaccination; 0.72% had 1 vaccine dose; 1.25% had 2 vaccine doses; and 2.22% had 3 vaccines. Notably, no severe infections nor deaths were recorded for those with 4 vaccine doses. Across the two mild categories (making up over 90% of infections in each vaccine bin), a dose-response relationship is observed.

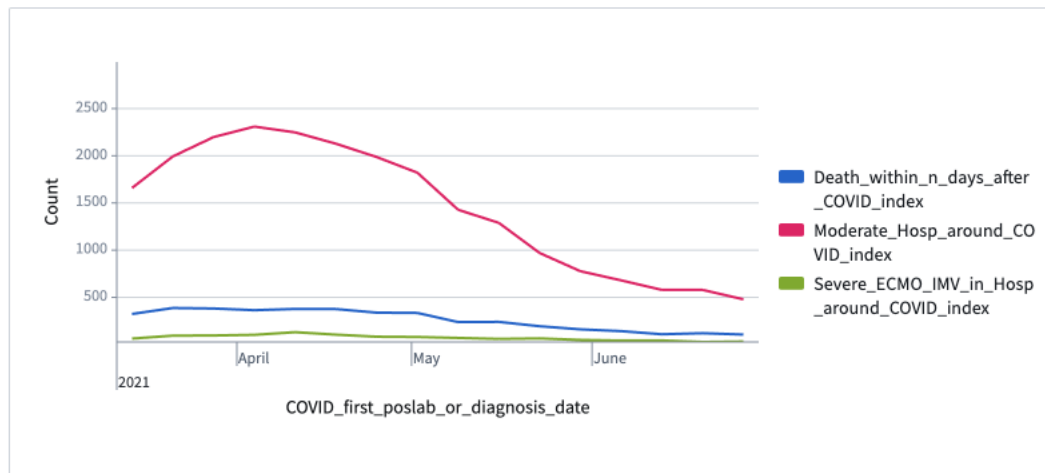


US Severity Type Percentage by Vaccination Count, FallWinter 2020



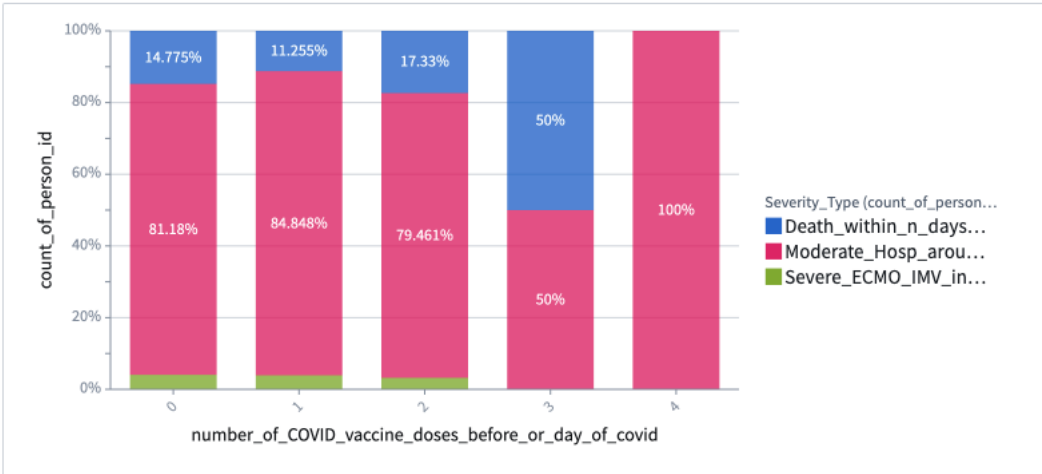
Considering only those who were hospitalized during the ‘Alpha/Vax’ epoch (28,460 infections), 81.25% of infections (n=23,124) were considered moderate; 4.02% (n=1,143) severe; and 14.73% (n=4,193) died within 60 days. The mean length of hospitalization during this inferred epoch was 6.96 days; this increased to 8.47 days for “severe” infections.

US Hospitalized Severity Counts Over Time, Alpha



Taking into account COVID vaccination status for those hospitalized, the majority of infections were considered moderate regardless of vaccination status (81.18% for no vaccination; 84.85% for 1 vaccine dose; 79.46% for 2 vaccine doses; 50% for 3 vaccine doses; and 100% for 4 vaccine doses). For those hospitalized with severe outcomes, 4.04% had no vaccination; 3.90% had 1 vaccine dose; and 3.21% had 2 vaccine doses. For hospitalized infections that resulted in death, 14.78% had no vaccination; 11.26% had 1 vaccine dose; 17.33% had 2 vaccine doses; and 50% had 3 vaccine doses. Notably, no one in our dataset with 4 vaccine doses at this time had severe infections or deaths related to their infection, and no one with 3 vaccines had severe infections. Excluding the 50% deaths for those with 3 vaccine doses, a dose response relationship is evident.

US Hospitalized Severity Type Percentage by Vaccination Count, Alpha

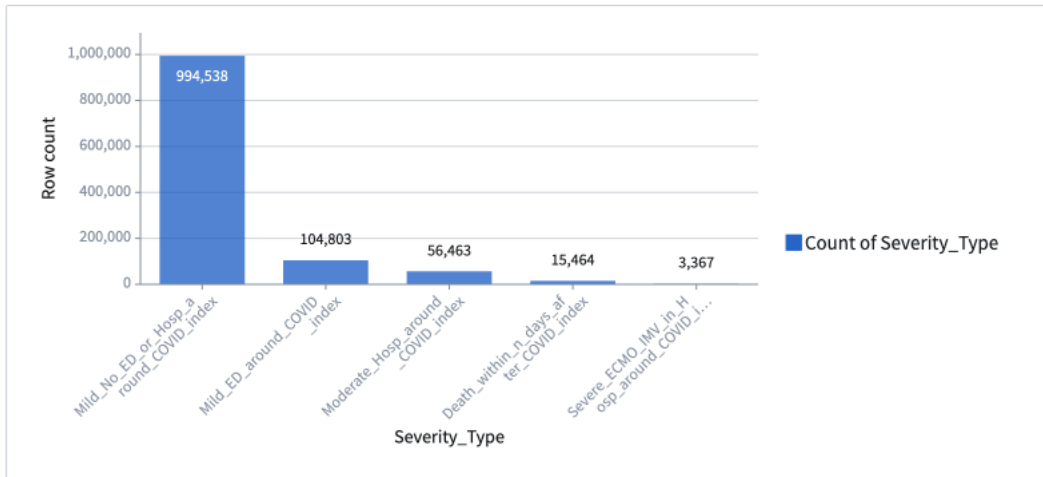


**Delta B.1.617.2 period: 2021-07-01 to 2021-12-01**

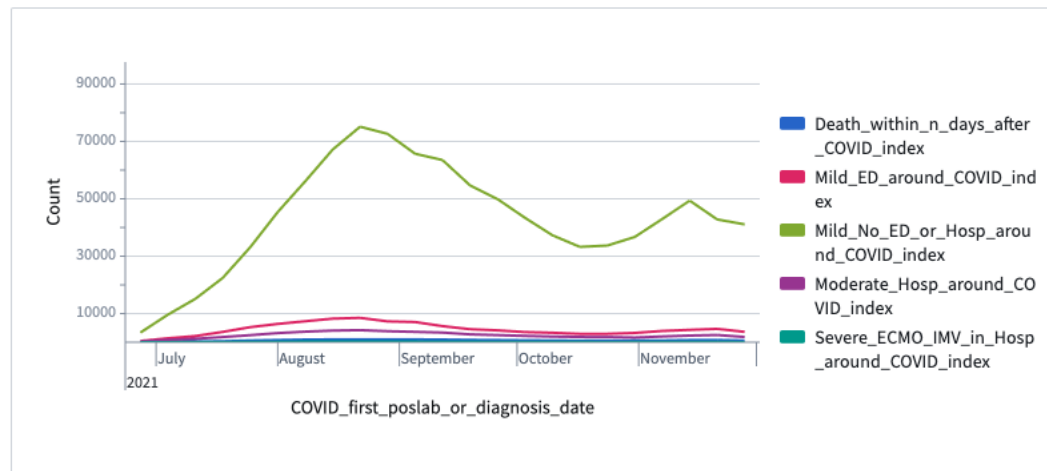
US

1,174,635 COVID-positive infections during the inferred 'Delta/B.1.617.2' epoch (2021-07-01 to 2021-12-01) were captured in our dataset. Of which 994,538 (84.67%) were mild and did not require an ED visit or hospitalization; 104,803 (8.92%) were considered mild with an ED visit; 56,463 (4.81%) were considered moderate and required hospitalization; 3,367 (0.29%) were considered severe, requiring ECMO/IMV; and 15,464 (1.32%) died within 60 days of their infection.

US Severity Counts, Delta

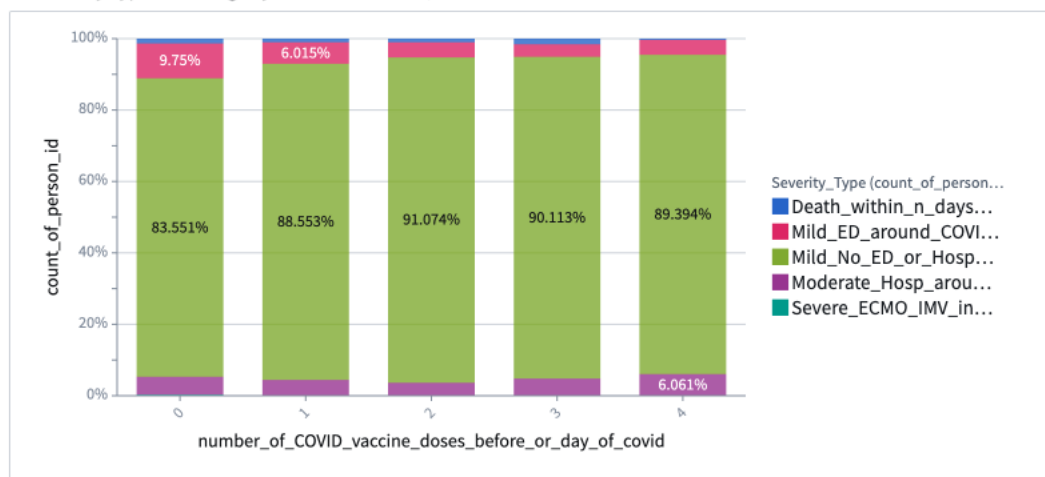


US Severity Counts Over Time, Delta



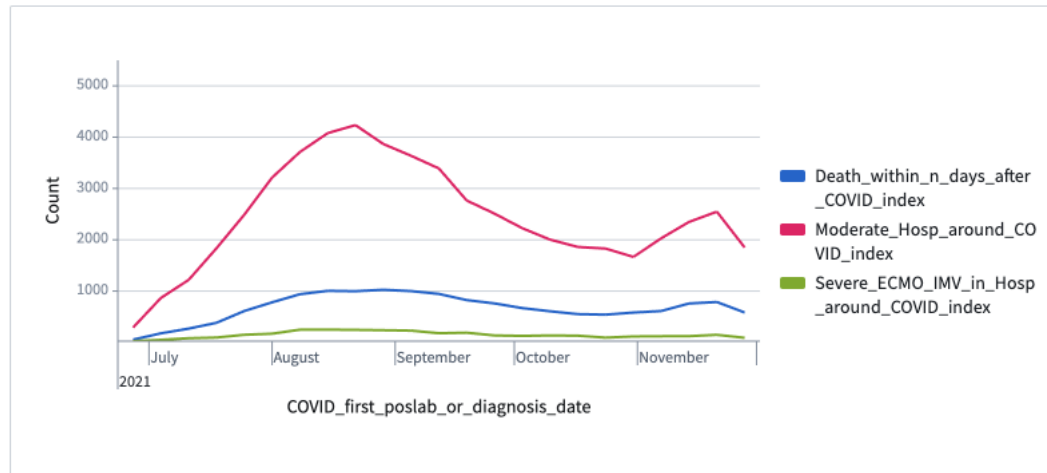
Taking into account COVID vaccination status, most infections were still mild, not requiring an ED visit or hospitalization, regardless of vaccination status or count (83.55% for no vaccination; 88.55% for 1 vaccine dose; 91.07% for 2 vaccine doses; 90.11% for 3 vaccine doses; and 89.39% for 4 vaccine doses). For mild infections requiring an ED visit, 9.75% had no vaccination; 6.02% had 1 vaccine dose; 4.26% had 2 vaccines doses; 3.51% had 3 vaccine doses; and 4.17% had 4 vaccine doses. For moderate infections requiring hospitalization, 5.01% had no vaccination; 4.24% had 1 vaccine dose; 3.57% had 2 vaccine doses; 4.77% had 3 vaccine doses; and 6.06% had 4 vaccine doses. For severe infections requiring ECMO/IMV, 0.32% had no vaccination; 0.18% had 1 vaccine dose; 0.08% had 2 vaccines; and 0.04% had 3 vaccines. For infections resulting in death, 1.37% had no vaccination; 1.01% had 1 vaccine dose; 1.02% had 2 vaccine doses; 1.57% had 3 vaccines; and 0.38% had 4 vaccines. Overall, the dose response relationship between increasing vaccine doses and increasing mild illness is evident.

US Severity Type Percentage by Vaccination Count, Delta



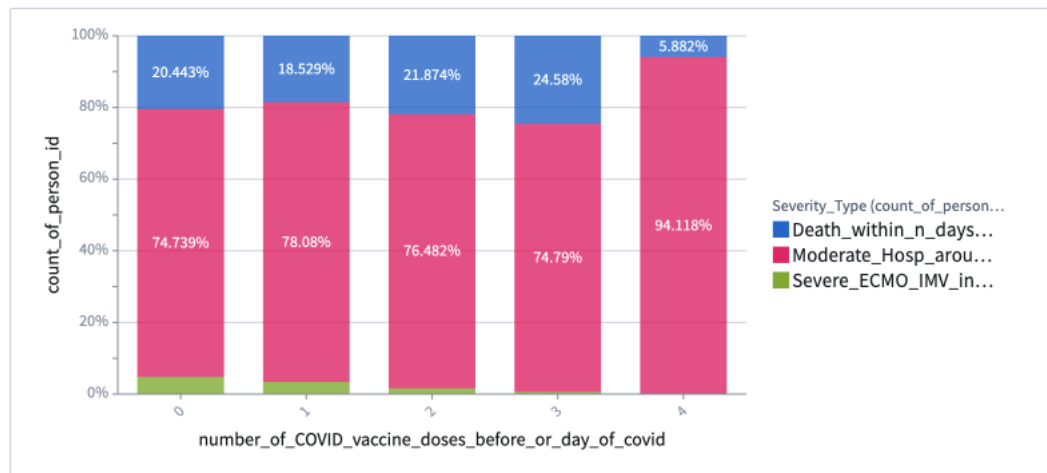
Considering only those who were hospitalized during the 'Delta/B.1.617.2' epoch (75,294 infections), 74.99% of infections (n=56,463) were considered moderate; 4.47% (n=3,367) severe; and 20.54% (n=15,464) died within 60 days. The mean length of hospitalization during this inferred epoch was 7.65 days; this increased to 11.44 days for "severe" infections.

US Hospitalized Severity Counts Over Time, Delta



Taking into account COVID vaccination status for those hospitalized, the majority of infections were considered moderate regardless of vaccination status (74.74% for no vaccination; 78.08% for 1 vaccine dose; 76.48% for 2 vaccine doses; 74.79% for 3 vaccine doses; and 94.12% for 4 vaccine doses. For those hospitalized with severe outcomes, 4.82% had no vaccination; 3.39% had 1 vaccine dose; 1.64% had 2 vaccine doses; and 0.63% had 3 vaccine doses. For hospitalized infections that resulted in death, 20.44% had no vaccination; 18.53% had 1 vaccine dose; 21.87% had 2 vaccine doses; 24.58% had 3 vaccine doses; and 5.88% had 4 vaccine doses. For this epoch, it appears severe infection had a dose-response relationship with vaccination, however deaths were very high and didn't seem to be affected by vaccination (except perhaps for 4 doses).

US Hospitalized Severity Type Percentage by Vaccination Count, Delta



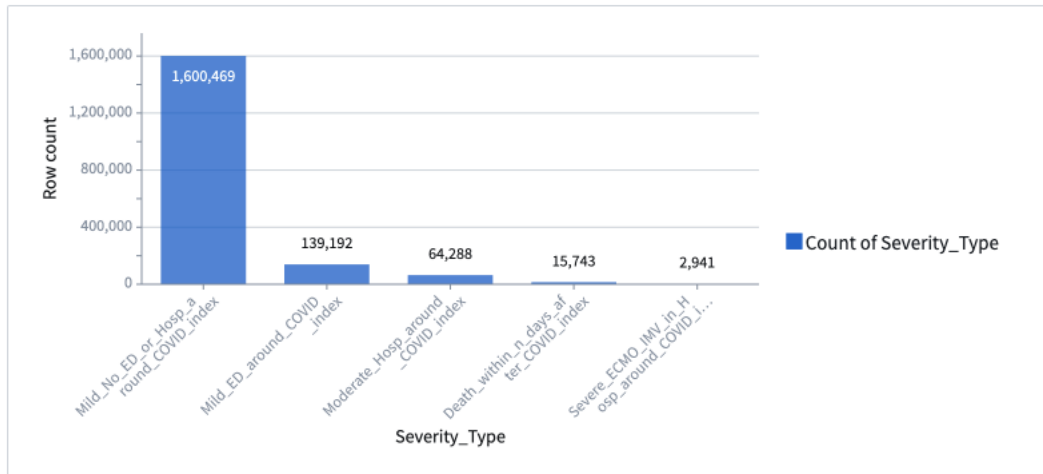
**BA.1/BA.2.75 period: 2021-12-01 to 2022-03-15**

US

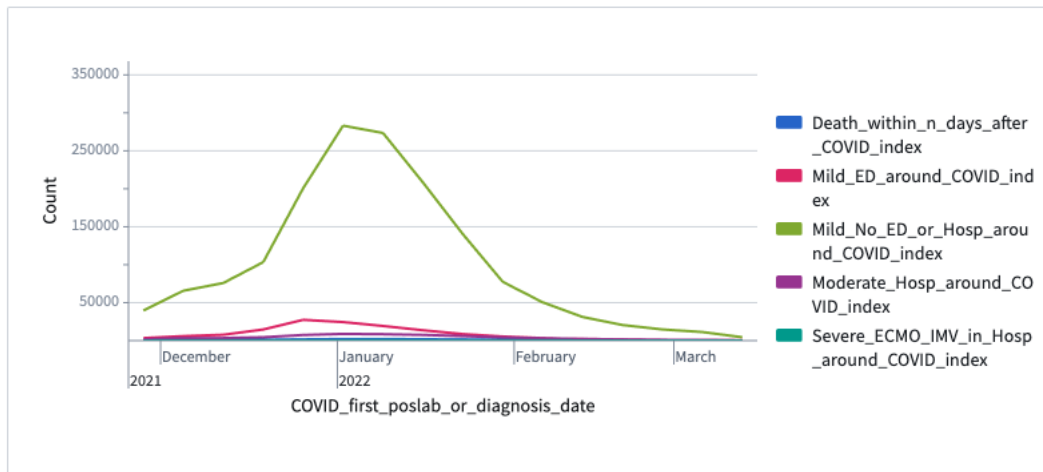
1,822,633 COVID-positive infections during the inferred 'BA.1/BA.2.75' epoch (2021-12-01 to 2022-03-15) were captured in our dataset. Of which 1,600,469 (87.81%) were mild and did not require an ED visit or hospitalization; 139,192 (7.64%) were considered mild with an ED visit; 64,288 (3.53%) were considered moderate and required hospitalization; 2,941 (0.16%) were

considered severe, requiring ECMO/IMV; and 15,743 (0.86%) died within 60 days of their infection.

US Severity Counts, BA.1/BA.2.75

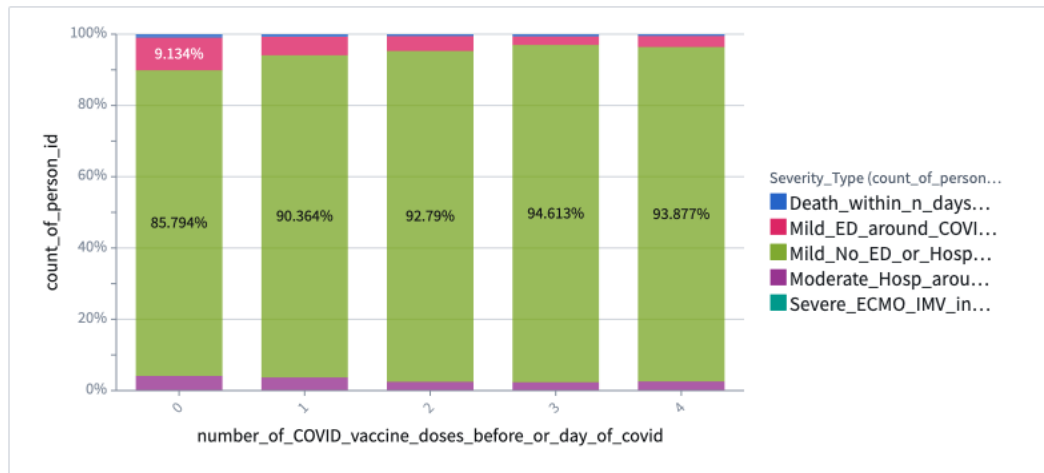


US Severity Counts Over Time, BA.1/BA.2.75



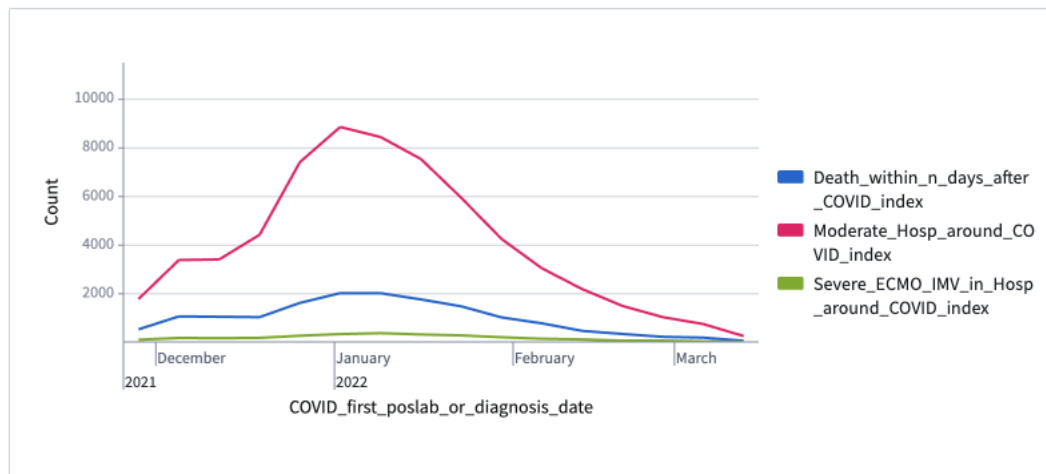
Taking into account COVID vaccination status, most infections were still mild, not requiring an ED visit or hospitalization, regardless of vaccination status or count (85.79% for no vaccination; 90.36% for 1 vaccine dose; 92.79% for 2 vaccine doses; 94.61% for 3 vaccine doses; and 93.88% for 4 vaccine doses). For mild infections requiring an ED visit, 9.13% had no vaccination; 5.18% had 1 vaccine dose; 4.16% had 2 vaccines doses; 2.42% had 3 vaccine doses; and 3.06% had 4 vaccine doses. For moderate infections requiring hospitalization, 3.91% had no vaccination; 3.57% had 1 vaccine dose; 2.41% had 2 vaccine doses; 2.28% had 3 vaccine doses; and 2.50% had 4 vaccine doses. For severe infections requiring ECMO/IMV, 0.20% had no vaccination; 0.14% had 1 vaccine dose; 0.07% had 2 vaccines; 0.05% had 3 vaccines; and 0.04% had 4 vaccine doses. For infections resulting in death, 0.96% had no vaccination; 0.75% had 1 vaccine dose; 0.57% had 2 vaccine doses; 0.63% had 3 vaccines; and 0.51% had 4 vaccines. Overall, the dose response relationship between increasing vaccine doses and increasing mild illness is evident.

US Severity Type Percentage by Vaccination Count, BA.1/BA.2.75



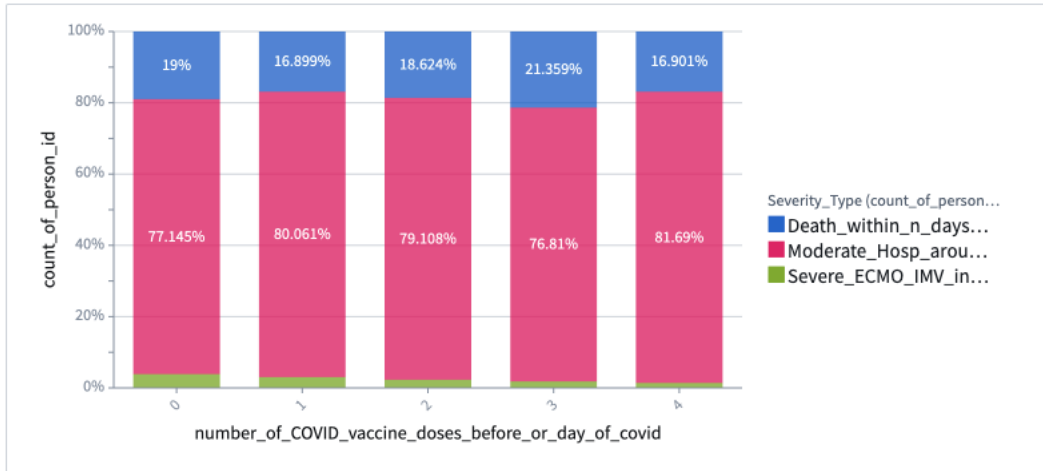
Considering only those who were hospitalized during the ‘BA.1/BA.2.75’ epoch (82,972 infections), 77.48% of infections (n=64,288) were considered moderate; 3.54% (n=2,941) severe; and 18.97% (n=15,743) died within 60 days. The mean length of hospitalization during this inferred epoch was 6.82 days; this increased to 8.92 days for “severe” infections.

US Hospitalized Severity Counts Over Time, BA.1/BA.2.75



Taking into account COVID vaccination status for those hospitalized, the majority of infections were considered moderate regardless of vaccination status (77.15% for no vaccination; 80.06% for 1 vaccine dose; 79.11% for 2 vaccine doses; 76.81% for 3 vaccine doses; and 81.69% for 4 vaccine doses. For those hospitalized with severe outcomes, 3.86% had no vaccination; 3.04% had 1 vaccine dose; 2.27% had 2 vaccine doses; 1.83% had 3 vaccine doses; and 1.41% had 4 vaccine doses. For hospitalized infections that resulted in death, 19.00% had no vaccination; 16.90% had 1 vaccine dose; 18.62% had 2 vaccine doses; 21.36% had 3 vaccine doses; and 16.90% had 4 vaccine doses. Similarly to the Delta epoch, this BA.1/BA.2.75 epoch, it appears severe infection had a dose-response relationship with vaccination, however deaths remained very high and didn’t seem to be affected by vaccination.

US Hospitalized Severity Type Percentage by Vaccination Count, BA.1/BA.2.75

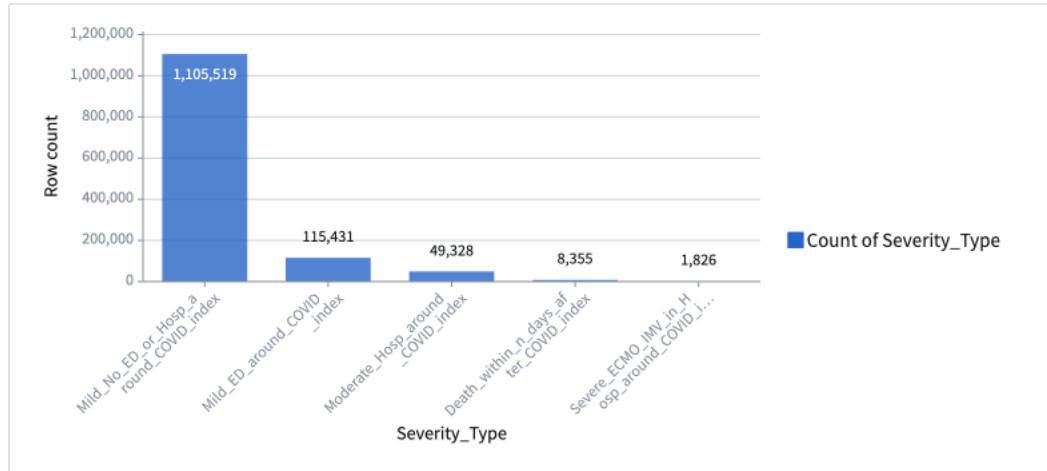


**BA.4/5 period: 2022-03-15 to 2022-10-31**

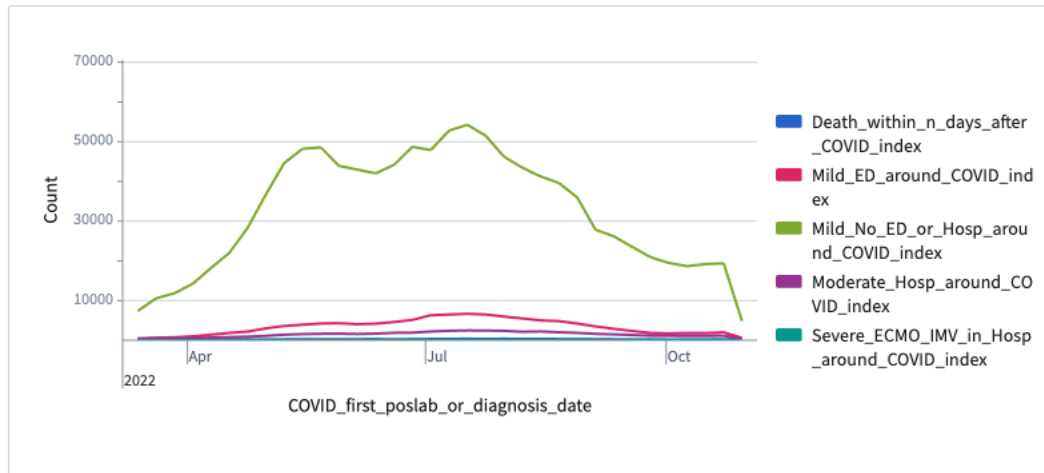
US

1,280,459 COVID-positive infections during the inferred 'BA.4/5' epoch (2022-03-15 to 2022-10-31) were captured in our dataset. Of which 1,105,519 (86.34%) were mild and did not require an ED visit or hospitalization; 115,431 (9.01%) were considered mild with an ED visit; 49,328 (3.85%) were considered moderate and required hospitalization; 1,826 (0.14%) were considered severe, requiring ECMO/IMV; and 8,355 (0.65%) died within 60 days of their infection.

US Severity Counts, BA.4/5

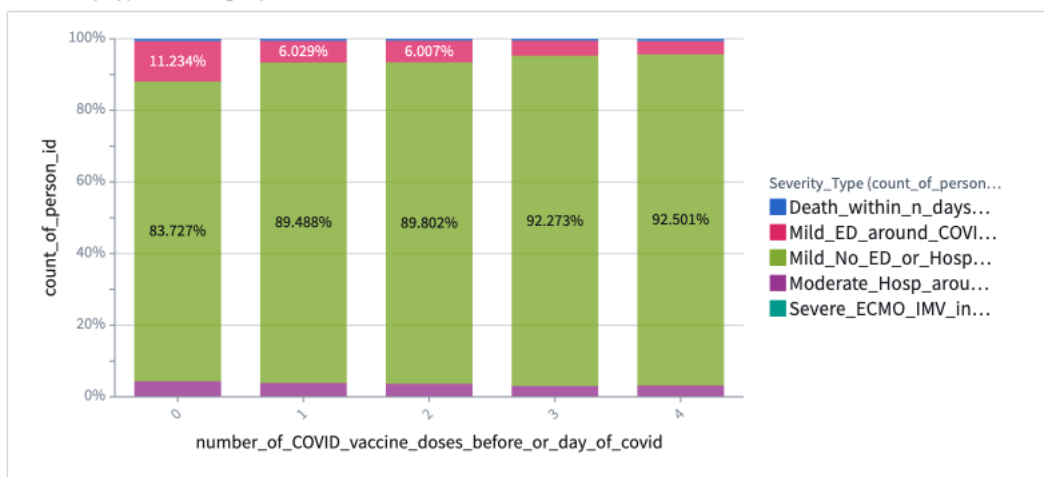


US Severity Counts Over Time, BA.4/5



Taking into account COVID vaccination status, most infections were still mild, not requiring an ED visit or hospitalization, regardless of vaccination status or count (83.73% for no vaccination; 89.49% for 1 vaccine dose; 89.80% for 2 vaccine doses; 92.27% for 3 vaccine doses; and 92.50% for 4 vaccine doses). For mild infections requiring an ED visit, 11.23% had no vaccination; 6.03% had 1 vaccine dose; 6.01% had 2 vaccines doses; 4.16% had 3 vaccine doses; and 3.63% had 4 vaccine doses. For moderate infections requiring hospitalization, 4.17% had no vaccination; 3.76% had 1 vaccine dose; 3.53% had 2 vaccine doses; 2.96% had 3 vaccine doses; and 3.10% had 4 vaccine doses. For severe infections requiring ECMO/IMV, 0.17% had no vaccination; 0.12% had 1 vaccine dose; 0.10% had 2 vaccines; 0.06% had 3 vaccines; and 0.09% had 4 vaccine doses. For infections resulting in death, 0.70% had no vaccination; 0.60% had 1 vaccine dose; 0.56% had 2 vaccine doses; 0.54% had 3 vaccines; and 0.69% had 4 vaccines. Overall, the dose response relationship between increasing vaccine doses and increasing mild illness is evident.

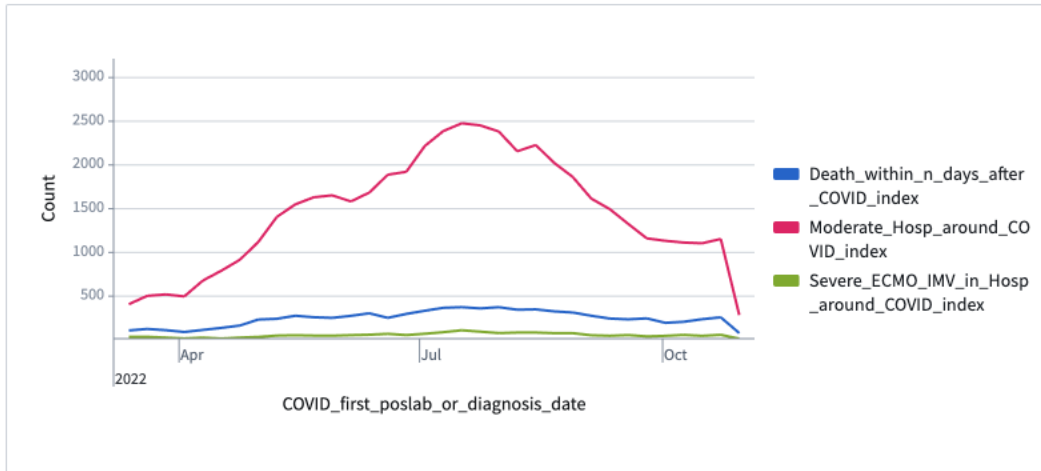
US Severity Type Percentage by Vaccination Count, BA.4/5



Considering only those who were hospitalized during the 'BA.4/5' epoch (59,509 infections), 82.89% of infections (n=49,328) were considered moderate; 3.07% (n=1,826) severe; and 14.04% (n=8,355) died within 60 days. The mean length of hospitalization during this inferred epoch was 5.72 days; this increased to 6.59 days for "severe" infections.

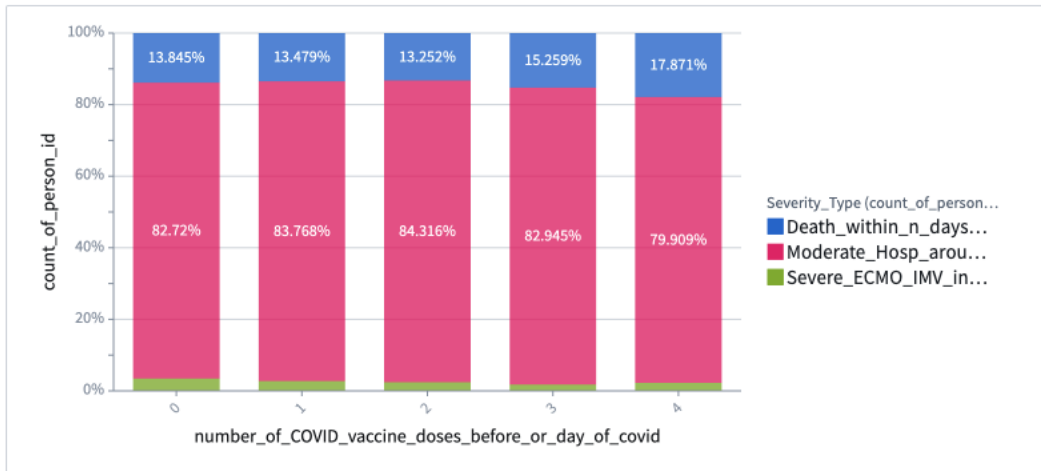


US Hospitalized Severity Counts Over Time, BA.4/5



Taking into account COVID vaccination status for those hospitalized, the majority of infections were considered moderate regardless of vaccination status (82.72% for no vaccination; 83.77% for 1 vaccine dose; 84.32% for 2 vaccine doses; 82.95% for 3 vaccine doses; and 79.91% for 4 vaccine doses. For those hospitalized with severe outcomes, 3.44% had no vaccination; 2.75% had 1 vaccine dose; 2.43% had 2 vaccine doses; 1.80% had 3 vaccine doses; and 2.22% had 4 vaccine doses. For hospitalized infections that resulted in death, 13.85% had no vaccination; 13.48% had 1 vaccine dose; 13.25% had 2 vaccine doses; 15.26% had 3 vaccine doses; and 17.87% had 4 vaccine doses. In this epoch, it appears severe infection had a dose-response relationship with vaccination, however deaths did not.

US Hospitalized Severity Type Percentage by Vaccination Count, BA.4/5



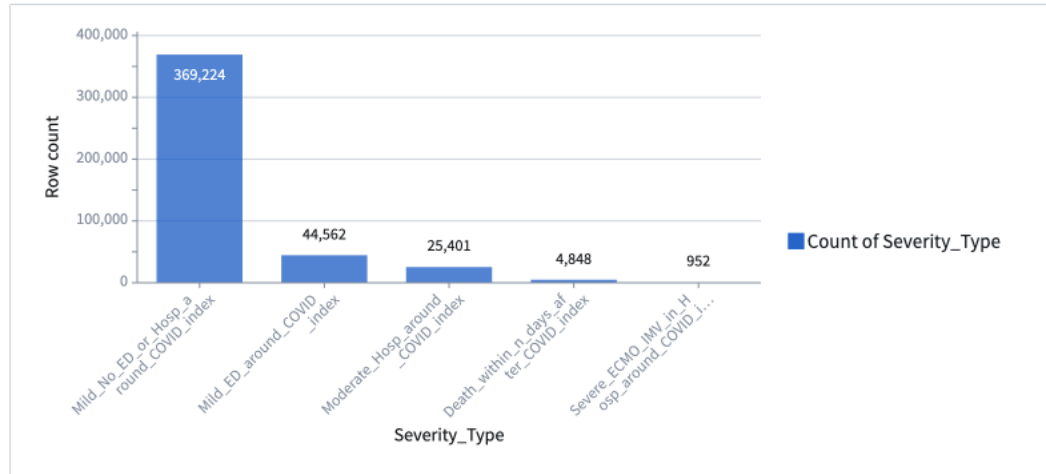
**XBB/BQ.1.1 period: 2022-10-31 to 2023-03-15**

US

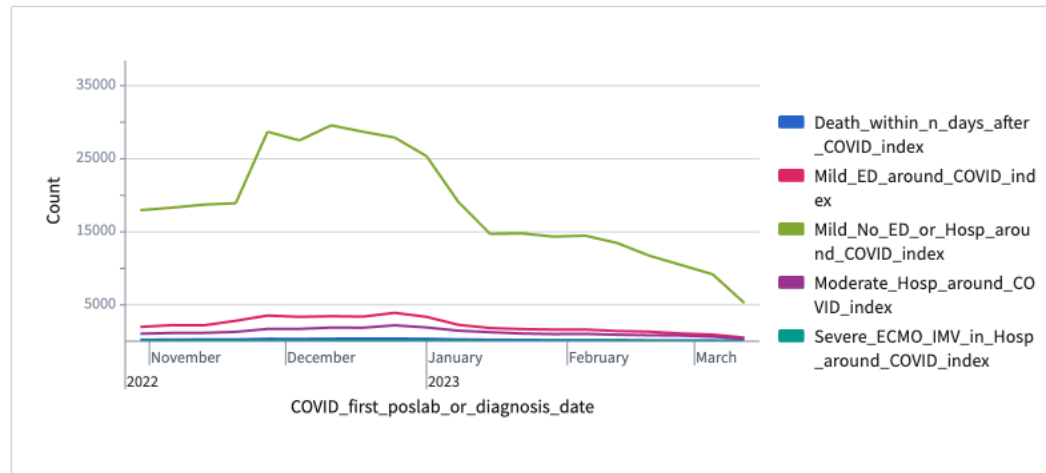
444,987 COVID-positive infections during the inferred 'XBB/BQ.1.1' epoch (2022-10-31 to 2023-03-15) were captured in our dataset. Of which 369,224 (82.97%) were mild and did not require an ED visit or hospitalization; 44,562 (10.01%) were considered mild with an ED visit; 25,401

(5.71%) were considered moderate and required hospitalization; 952 (0.21%) were considered severe, requiring ECMO/IMV; and 4,848 (1.09%) died within 60 days of their infection.

US Severity Counts, XBB/BQ.1.1

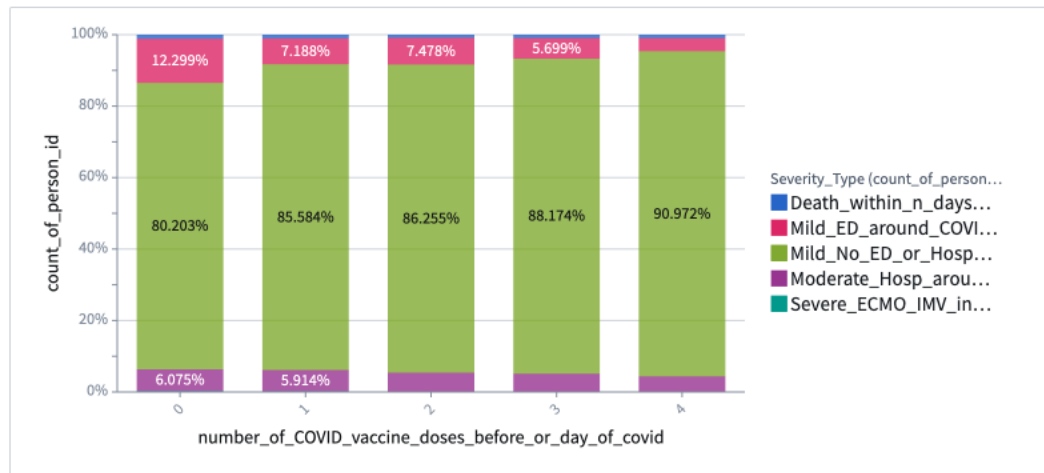


US Severity Counts Over Time, XBB/BQ.1.1



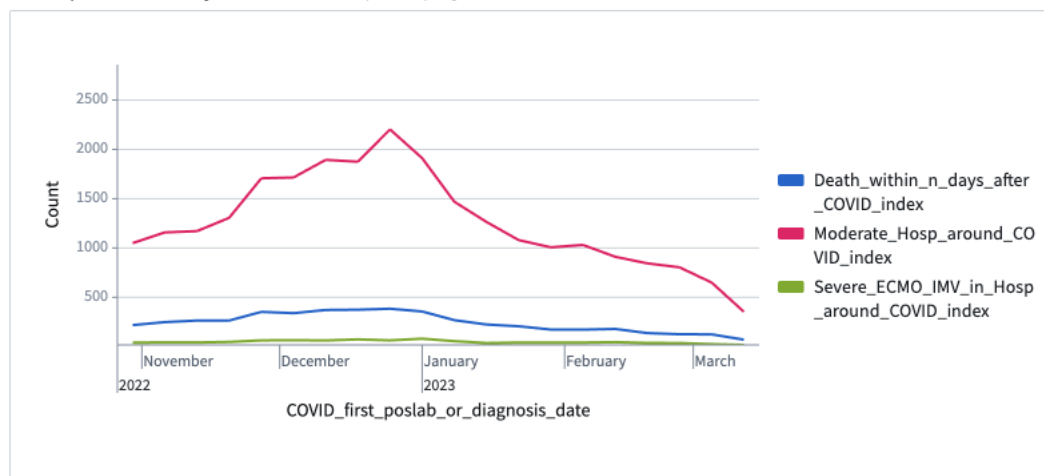
Taking into account COVID vaccination status, most infections were still mild, not requiring an ED visit or hospitalization, regardless of vaccination status or count (80.20% for no vaccination; 85.58% for 1 vaccine dose; 86.26% for 2 vaccine doses; 88.17% for 3 vaccine doses; and 90.97% for 4 vaccine doses). For mild infections requiring an ED visit, 12.30% had no vaccination; 7.19% had 1 vaccine dose; 7.48% had 2 vaccines doses; 5.70% had 3 vaccine doses; and 3.65% had 4 vaccine doses. For moderate infections requiring hospitalization, 6.08% had no vaccination; 5.91% had 1 vaccine dose; 5.28% had 2 vaccine doses; 5.01% had 3 vaccine doses; and 4.30% had 4 vaccine doses. For severe infections requiring ECMO/IMV, 0.26% had no vaccination; 0.24% had 1 vaccine dose; 0.12% had 2 vaccines; 0.12% had 3 vaccines; and 0.10% had 4 vaccine doses. For infections resulting in death, 1.16% had no vaccination; 1.08% had 1 vaccine dose; 0.87% had 2 vaccine doses; 1.10% had 3 vaccines; and 0.97% had 4 vaccines. Overall, the dose response relationship between increasing vaccine doses and increasing mild illness is evident across categories.

US Severity Type Percentage by Vaccination Count, XBB/BQ.1.1



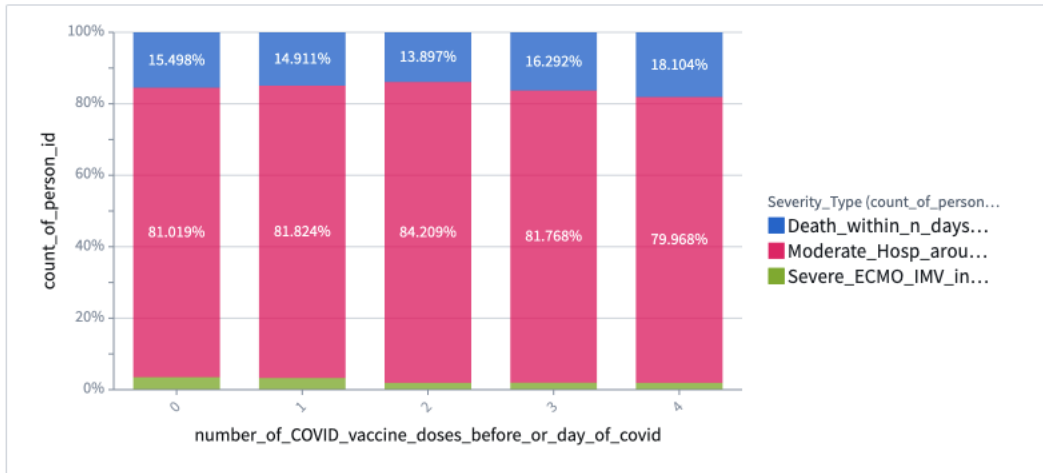
Considering only those who were hospitalized during the 'XBB/BQ.1.1.' epoch (31,201 infections), 81.41% of infections (n=25,401) were considered moderate; 3.05% (n=952) severe; and 15.54% (n=4,848) died within 60 days. The mean length of hospitalization during this inferred epoch was 5.85 days; this increased to 6.37 days for "severe" infections.

US Hospitalized Severity Counts Over Time, WXBB/BQ.1.1



Taking into account COVID vaccination status for those hospitalized, the majority of infections were considered moderate regardless of vaccination status (81.02% for no vaccination; 81.82% for 1 vaccine dose; 84.21% for 2 vaccine doses; 81.77% for 3 vaccine doses; and 79.97% for 4 vaccine doses. For those hospitalized with severe outcomes, 3.48% had no vaccination; 3.27% had 1 vaccine dose; 1.89% had 2 vaccine doses; 1.94% had 3 vaccine doses; and 1.93% had 4 vaccine doses. For hospitalized infections that resulted in death, 15.50% had no vaccination; 14.91% had 1 vaccine dose; 13.90% had 2 vaccine doses; 16.29% had 3 vaccine doses; and 18.10% had 4 vaccine doses. In this epoch, it appears severe infection had a dose-response relationship with vaccination, however deaths did not.

US Hospitalized Severity Type Percentage by Vaccination Count, XBB/BQ.1.1

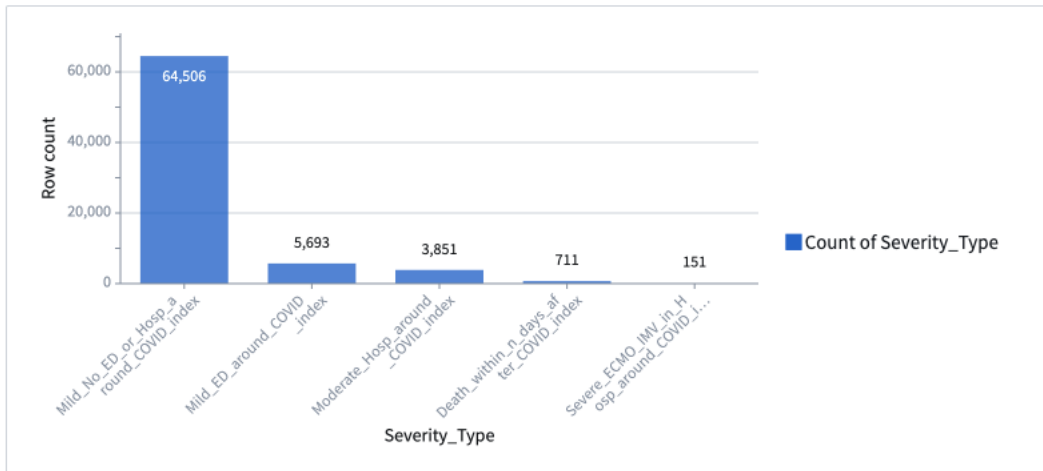


**POST-XBB period: 2023-03-15 to 2023-07-31**

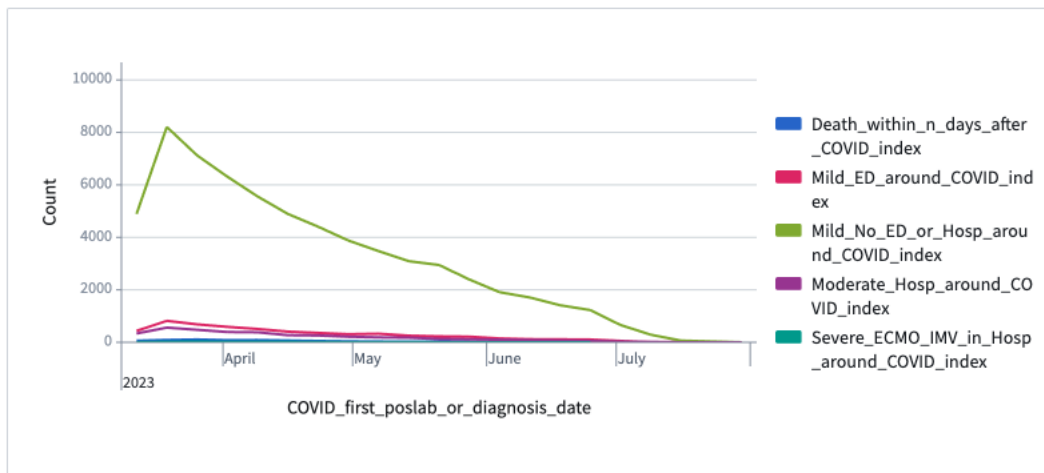
US

74,912 COVID-positive infections during the inferred 'POST-XBB epoch (2023-03-15 to 2023-07-31) were captured in our dataset. Of which 64,506 (86.11%) were mild and did not require an ED visit or hospitalization; 5,693 (7.60%) were considered mild with an ED visit; 3,851 (5.14%) were considered moderate and required hospitalization; 151 (0.20%) were considered severe, requiring ECMO/IMV; and 711 (0.95%) died within 60 days of their infection.

US Severity Counts, Post-XBB/BQ.1.1

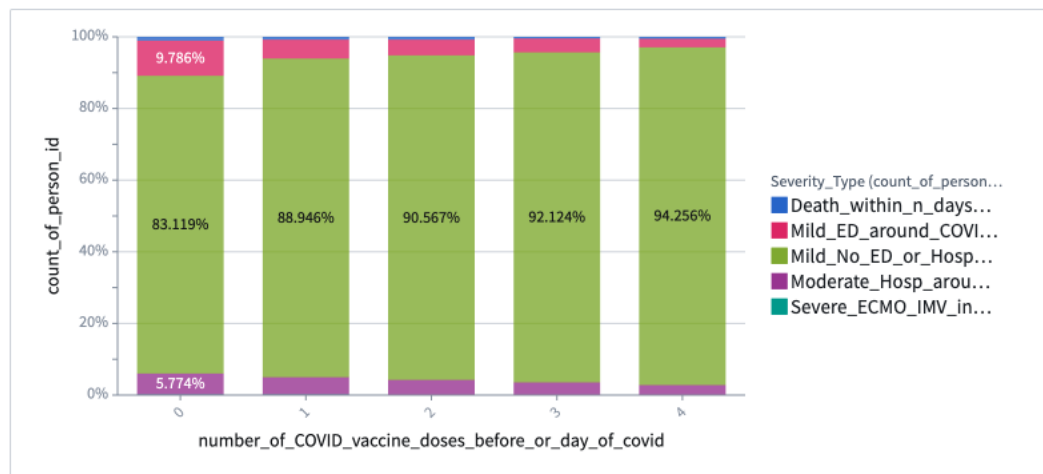


US Severity Counts Over Time, Post-XBB/BQ.1.1



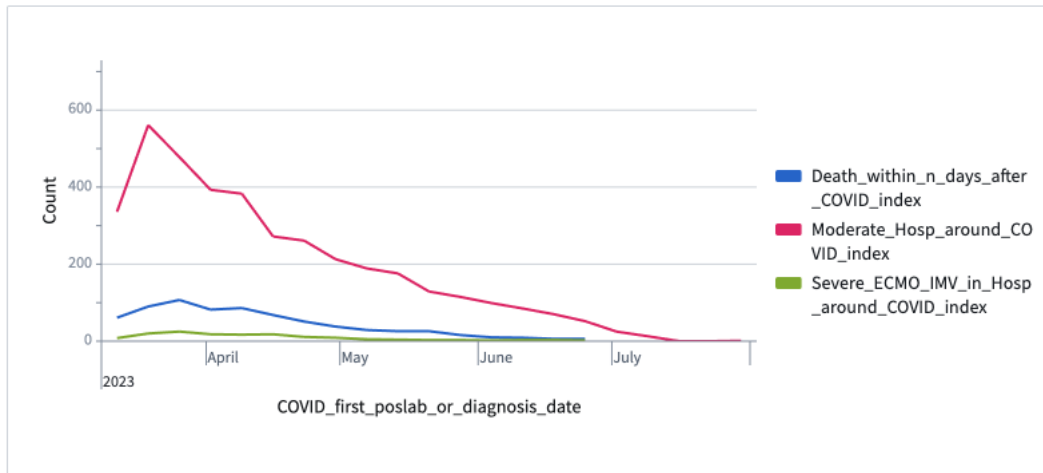
Taking into account COVID vaccination status, most infections were still mild, not requiring an ED visit or hospitalization, regardless of vaccination status or count (83.12% for no vaccination; 88.95% for 1 vaccine dose; 90.57% for 2 vaccine doses; 92.12% for 3 vaccine doses; and 94.26% for 4 vaccine doses). For mild infections requiring an ED visit, 9.79% had no vaccination; 5.26% had 1 vaccine dose; 4.39% had 2 vaccines doses; 3.87% had 3 vaccine doses; and 2.37% had 4 vaccine doses. For moderate infections requiring hospitalization, 5.77% had no vaccination; 4.78% had 1 vaccine dose; 4.16% had 2 vaccine doses; 3.39% had 3 vaccine doses; and 2.71% had 4 vaccine doses. For severe infections requiring ECMO/IMV, 0.24% had no vaccination; 0.22% had 1 vaccine dose; 0.08% had 2 vaccines; 0.15% had 3 vaccines; and 0.10% had 4 vaccine doses. For infections resulting in death, 1.08% had no vaccination; 0.80% had 1 vaccine dose; 0.80% had 2 vaccine doses; 0.46% had 3 vaccines; and 0.57% had 4 vaccines. Overall, the dose response relationship between increasing vaccine doses and increasing mild illness is evident across categories.

US Severity Type Percentage by Vaccination Count, Post-XBB/BQ.1.1



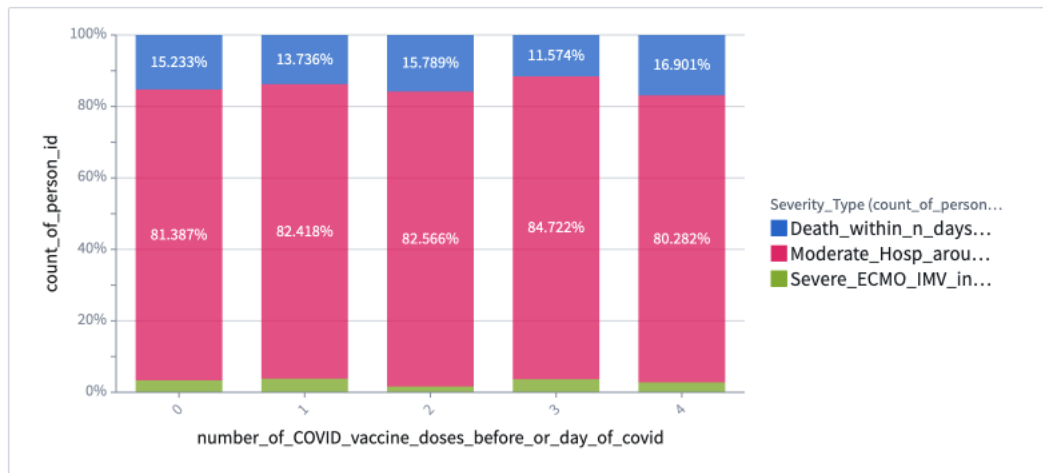
Considering only those who were hospitalized during the 'XBB/BQ.1.1.' epoch (31,201 infections), 81.41% of infections (n=25,401) were considered moderate; 3.05% (n=952) severe; and 15.54% (n=4,848) died within 60 days. The mean length of hospitalization during this inferred epoch was 5.85 days; this increased to 6.37 days for "severe" infections.

US Hospitalized Severity Counts Over Time, Post-XBB/BQ.1.1



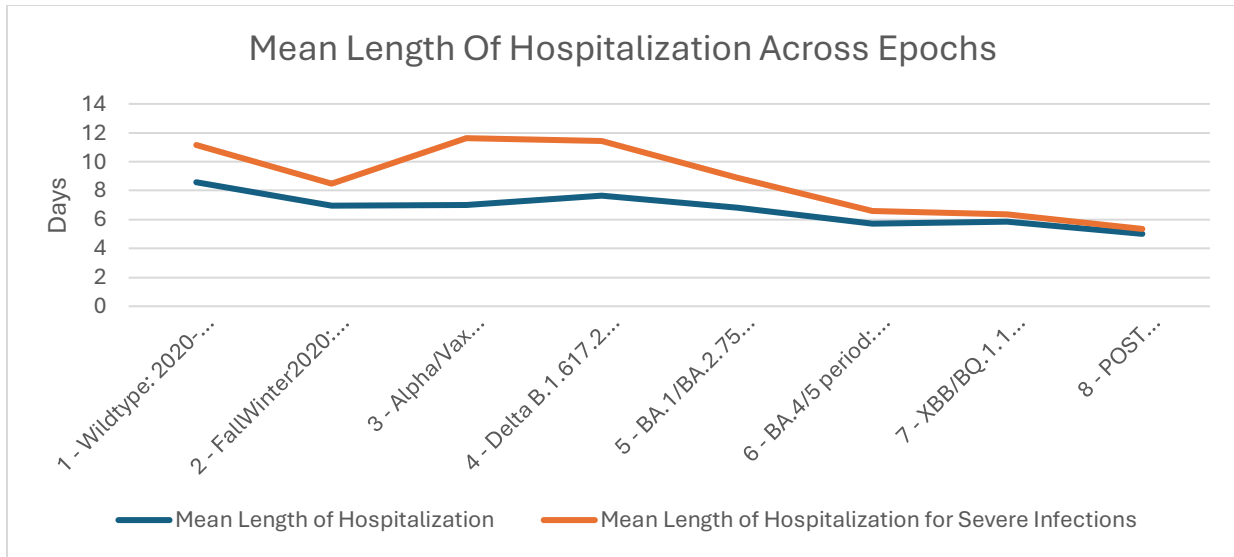
Taking into account COVID vaccination status for those hospitalized, the majority of infections were considered moderate regardless of vaccination status (81.40% for no vaccination; 82.42% for 1 vaccine dose; 82.57% for 2 vaccine doses; 84.72% for 3 vaccine doses; and 80.28% for 4 vaccine doses. For those hospitalized with severe outcomes, 3.38% had no vaccination; 3.85% had 1 vaccine dose; 1.65% had 2 vaccine doses; 3.70% had 3 vaccine doses; and 2.82% had 4 vaccine doses. For hospitalized infections that resulted in death, 15.23% had no vaccination; 13.74% had 1 vaccine dose; 15.79% had 2 vaccine doses; 11.57% had 3 vaccine doses; and 16.90% had 4 vaccine doses. In this epoch, it appears severe infection and death no longer have a dose-response relationship with vaccination.

US Hospitalized Severity Type Percentage by Vaccination Count, Post-XBB/BQ.1.1



### Mean Length of Hospitalization

Mean length of hospitalization has decreased over time (from 8.58 days to 5.01 days). Mean length of hospitalization for severe infections has also decreased over time (from 11.63 days at its peak in Alpha to 5.35 days).



### Logistic Regression Results

In an effort to further investigate these severity metrics per epoch controlling for important covariates and potential confounders, logistic regression models were run for outcomes of “severe” (requiring ECMO/IMV) and “death”. Covariates and potential confounders included the following variables:

1. age\_at\_covid
2. sex
3. state
4. race
5. race\_ethnicity
6. BMI\_max\_observed\_or\_calculated\_before\_or\_day\_of\_covid
7. number\_of\_COVID\_vaccine\_doses\_before\_or\_day\_of\_covid
8. TUBERCULOSIS\_before\_or\_day\_of\_covid\_indicator
9. MILDLIVERDISEASE\_before\_or\_day\_of\_covid\_indicator
10. MODERATESEVERELIVERDISEASE\_before\_or\_day\_of\_covid\_indicator
11. THALASSEMIA\_before\_or\_day\_of\_covid\_indicator
12. RHEUMATOLOGICDISEASE\_before\_or\_day\_of\_covid\_indicator
13. DEMENTIA\_before\_or\_day\_of\_covid\_indicator
14. CONGESTIVEHEARTFAILURE\_before\_or\_day\_of\_covid\_indicator
15. SUBSTANCEUSEDISORDER\_before\_or\_day\_of\_covid\_indicator
16. DOWNSYNDROME\_before\_or\_day\_of\_covid\_indicator
17. KIDNEYDISEASE\_before\_or\_day\_of\_covid\_indicator
18. MALIGNANTCANCER\_before\_or\_day\_of\_covid\_indicator
19. DIABETESCOMPLICATED\_before\_or\_day\_of\_covid\_indicator
20. CEREBROVASCULARDISEASE\_before\_or\_day\_of\_covid\_indicator
21. PERIPHERALVASCULARDISEASE\_before\_or\_day\_of\_covid\_indicator
22. PREGNANCY\_before\_or\_day\_of\_covid\_indicator
23. HEARTFAILURE\_before\_or\_day\_of\_covid\_indicator

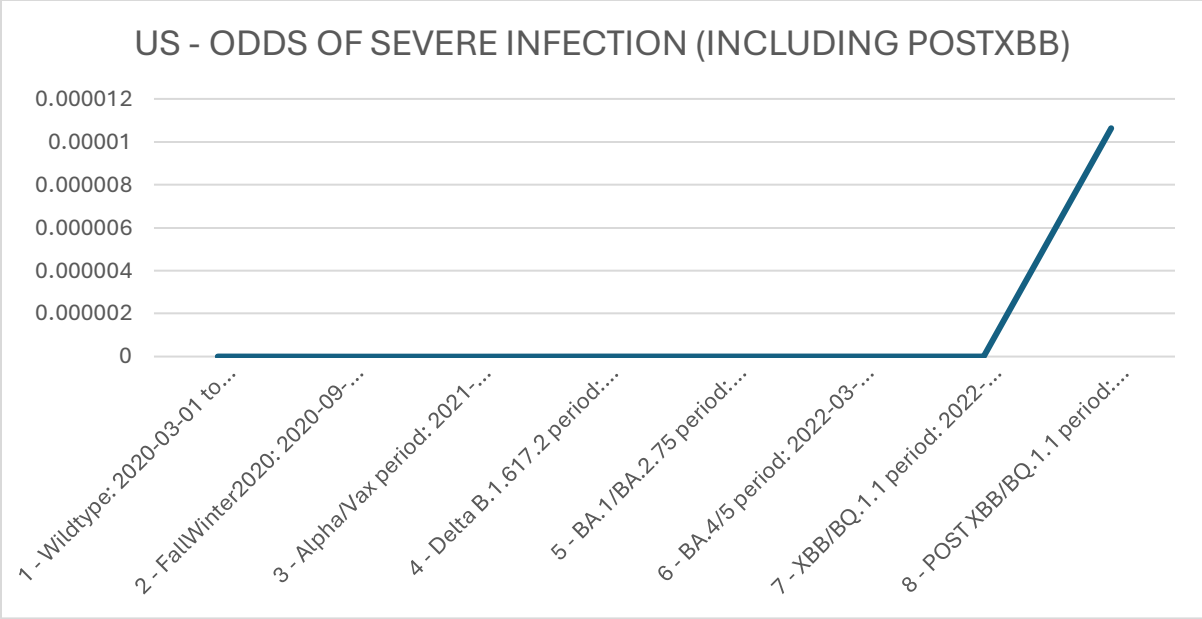
24. HEMIPLEGIAORPARAPLEGIA\_before\_or\_day\_of\_covid\_indicator
25. PSYCHOSIS\_before\_or\_day\_of\_covid\_indicator
26. OBESITY\_before\_or\_day\_of\_covid\_indicator
27. CORONARYARTERYDISEASE\_before\_or\_day\_of\_covid\_indicator
28. SYSTEMICCORTICOSTEROIDS\_before\_or\_day\_of\_covid\_indicator
29. DEPRESSION\_before\_or\_day\_of\_covid\_indicator
30. METASTATICSOLIDTUMORCANCERS\_before\_or\_day\_of\_covid\_indicator
31. HIVINFECTION\_before\_or\_day\_of\_covid\_indicator
32. CHRONICLUNGDISEASE\_before\_or\_day\_of\_covid\_indicator
33. PEPTICULCER\_before\_or\_day\_of\_covid\_indicator
34. SICKLECELLDISEASE\_before\_or\_day\_of\_covid\_indicator
35. MYOCARDIALINFARCTION\_before\_or\_day\_of\_covid\_indicator
36. DIABETESUNCOMPLICATED\_before\_or\_day\_of\_covid\_indicator
37. CARDIOMYOPATHIES\_before\_or\_day\_of\_covid\_indicator
38. HYPERTENSION\_before\_or\_day\_of\_covid\_indicator
39. OTHERIMMUNOCOMPROMISED\_before\_or\_day\_of\_covid\_indicator
40. Antibody\_Neg\_before\_or\_day\_of\_covid\_indicator
41. PULMONARYEMBOLISM\_before\_or\_day\_of\_covid\_indicator
42. TOBACCSMOKER\_before\_or\_day\_of\_covid\_indicator
43. SOLIDORGANORBLOODSTEMCELLTRANSPLANT\_before\_or\_day\_of\_covid\_indicator
44. Antibody\_Pos\_before\_or\_day\_of\_covid\_indicator

The intercept coefficient for each logistic regression model was exponentiated to transform log odds into odds ratios, facilitating comparison across epochs. Beta coefficients for demographics and comorbidities have not yet been interpreted or compared across epochs, nor have interactions terms been considered.

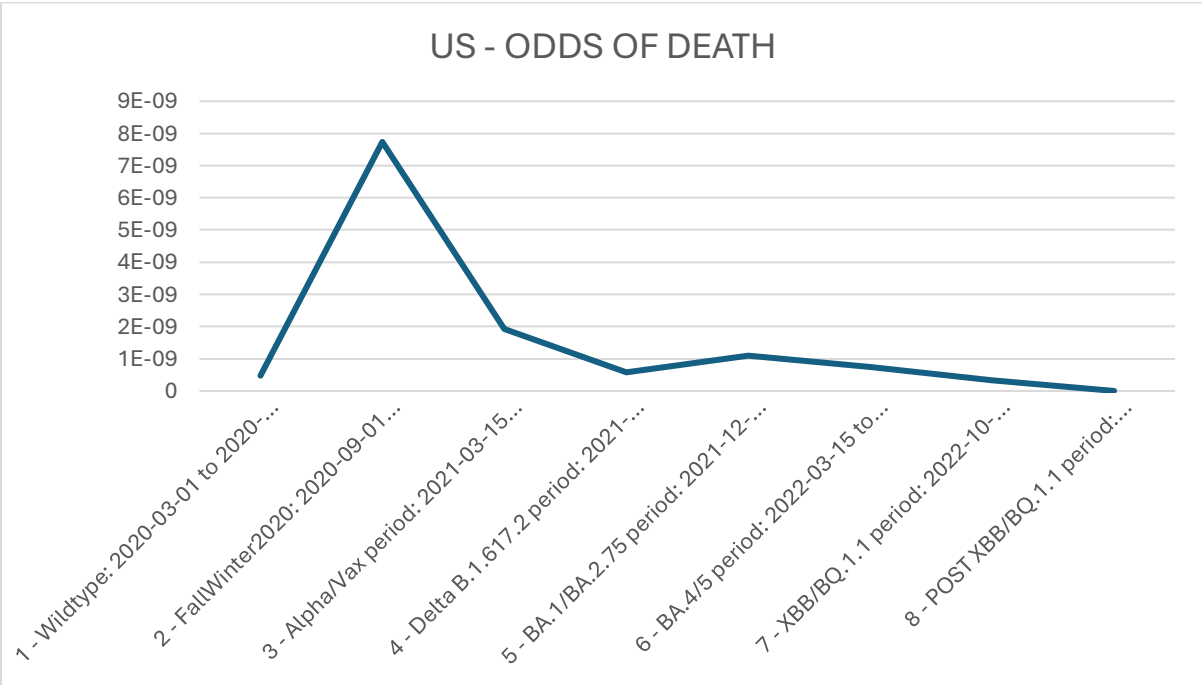
Although all odds ratios across models were found to be very small and less than 1, signifying reduced odds of each outcome, the relative magnitude of their effects can be ranked as follows:

- **Severe infections (ECMO, IMV):**
  1. PostXBB, 1.06E-05
  2. Alpha, 1.10E-10
  3. FallWinter2020, 1.08E-11
  4. Wildtype, 7.23E-19
  5. Delta, 5.87E-19
  6. BA.4/5, 4.66E-19
  7. XBB, 4.57E-19
  8. BA.1/2, 4.33E-19





- **Death:**
  1. FallWinter2020, 7.73609E-09
  2. Alpha, 1.93178E-09
  3. BA.1/2, 1.09775E-09
  4. BA.4/5, 7.403E-10
  5. Delta, 5.70162E-10
  6. Wildtype, 4.69153E-10
  7. XBB, 3.27347E-10
  8. PostXBB, 1.06E-17



## Conclusions

The vast majority of infections, regardless of epoch/major strain, were mild and did not require hospitalization. Risk of severe outcomes and death increase substantially if hospitalized.

Across all major inferred variants, a clear dose response relationship seen with vaccination and percentages of mild vs. moderate+ infections. Alpha produced more moderate infections. The data also show an uptick in XBB moderate infections. A higher percent of deaths is seen before mass vaccination period and during the Delta epoch. In general, a dose response relationship is seen with vaccinations and mild infections—the more vaccine doses one received, the milder their infections were. This was also evident across epochs until Post-XBB for severe infections. The picture is less clear for those who were hospitalized and ultimately died as a result of their relationship, however the overall percentage of deaths has decreased over time.

The mean length of hospitalization has decreased over time (from 8.58 days to 5.01 days). Mean length of hospitalization for severe infections has also decreased over time (from 11.63 days at its peak in Alpha to 5.35 days).

Taking into account (as best we can with N3C data) immune history and comorbidities in general:

- **Severe infections (ECMO, IMV):**
  - (PostXBB), Alpha, FallWinter2020, Wildtype, Delta, BA.4/5, XBB, BA.1/2
- **Death:**
  - FallWinter2020, Alpha, BA.1/2, BA.4/5, Delta, Wildtype, XBB, (PostXBB)

## Limitations

The key limitation to reiterate is that N3C is not considered a nationally representative sample, so there should be caution when interpreting results, particularly when it comes to the results' generalizability. To that regard, the EHR data used in N3C may vary in quality and completeness across different healthcare systems. Incomplete or inaccurate data could impact the validity of analyses and conclusions drawn from them.

N3C's data primarily comes from patients who sought out healthcare services during the pandemic, which could introduce selection bias. Those who did not seek healthcare or were asymptomatic may not be represented, leading to skewed findings. This is also likely affected by temporal issues, as changes in testing protocols, treatments, and healthcare practices during the pandemic may influence the patterns observed.

N3C data may not always capture all relevant confounding factors that could influence outcomes, such as socioeconomic status, access to healthcare, or undiagnosed comorbidities. Failure to account for these adequately can also lead to biased results.

And finally, another key limitation of this analysis is due to the lack of available genomic data in N3C, major strains were inferred per the dominant variant during a particular time period.

Despite these limitations, we have endeavored to account for these factors to the best of our ability, employing rigorous methodologies and transparent reporting practices to ensure the validity and reliability of our analyses using N3C data.

### **Acknowledgements:**

The analyses described in this report were conducted with data and tools accessed through the NCATS N3C Data Enclave (<https://covid.cd2h.org>) and N3C Attribution & Publication Policy v 1.2-2020-08-25b supported by NCATS U24 TR002306 and [insert additional funding agencies or sources and reference numbers]. This research was possible because of the patients whose information is included within the data and the organizations (<https://ncats.nih.gov/n3c/resources/data-contribution/data-transfer-agreement-signatories>) and scientists who have contributed to the on-going development of this community resource [<https://doi.org/10.1093/jamia/ocaa196>].

### **Reference:**

National Institutes of Health (NIH). National Center for Advancing Translational Sciences (NCATS). National COVID Cohort Collaborative Data Enclave Repository. Bethesda, Maryland: U.S. Department of Health and Human Services, National Institutes of Health, 2024, accessed Oct 2023-April 2024.  
<https://unite.nih.gov/workspace/compass/view/ri.compass.main.folder.48c78748-99fa-4fa1-9d39-abb305c51b25>