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Impact Of Sars-Cov-2 Variants On Vaccine Breakthrough Infections

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Abstract

SARS-CoV-2 variants of concern are defined by their increased intrinsic transmissibility and ability to evade immune recognition and neutralization, yet the relative importance of these factors in determining variant fitness in population settings is unclear. We hypothesize that as population level immunity has increased throughout the course of the pandemic, immune escape has played an increasingly important role in the emergence and sustained circulation of variants. Here, we use logistic regression models to estimate the odds of vaccine breakthrough infections for several major variants of concern in a population of Connecticut residents. We investigate the impact of immune escape on sustained variant circulation across 18 months of the pandemic and in four periods of variant emergence in the context of increasing vaccination uptake rates. We show significantly increased odds of vaccine breakthrough infections associated with the Omicron BA.1 variant relative to the Delta variant [2 vaccine doses ≥5 months adjusted OR: 2.093, 95% CI: 1.11 - 3.94 | 3 vaccine doses ≤5 months adjusted OR: 7.118, 95% CI: 1.44 - 35.17] as well as the Omicron BA.4 and BA.5 variants relative to the Omicron BA.2 variant [3 vaccine doses adjusted OR: 1.66, 95% CI: 1.01 - 2.73]. We also show significantly decreased odds of vaccine breakthrough infections associated with the Alpha variant relative to the pre-Alpha variant lineages [adjusted OR: 0.796, 95% CI: 0.73, 0.86] as well as decreasing age and female sex. These findings suggest immune escape played an important role in the emergence of the Omicron BA.1 variant and imply an important association between demographic characteristics and vaccine breakthrough infections.

Acknowledgements

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Finally, I'd like to thank the members of the Grubaugh Lab for providing a welcoming and collegial environment. Notably, I'd like to thank Dr. Grubaugh for giving me the opportunity to join his team and Dr. Vogels for taking me under her wing during my summer internship. The opportunity to work with such a uniquely talented group has been an unparalleled learning experience, and I am grateful to call each member both a colleague and a friend.

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Introduction

A defining characteristic of the ongoing COVID-19 pandemic has been the emergence and subsequent domination of novel SARS-CoV-2 lineages in the infection landscape. These variants, designated as Variants of Concern (VOC) by the World Health Organization (WHO), are characterized by in vitro evidence for enhanced intrinsic transmissibility and an increased ability to evade neutralizing antibodies resulting in vaccine breakthrough infections amongst previously immunized individuals[1]. Both increased transmissibility and immune escape offer a theoretical competitive advantage amongst co-circulating variants, however, it remains unclear how these in vitro factors translate to variant fitness in a dynamic population setting. Early in the pandemic, several lineages including the Beta, Gamma, and Epsilon variants evolved mutations in key sites associated with increased transmissibility or immune escape, yet these variants failed to outcompete their rivals and soon died out[2]. This early period of high co-circulation and competition was soon replaced by a distinct pattern of variants emerging, going on to account for a majority of new infections, and being replaced by a newly emergent variant with distinct phenotypic properties. Underlying these changes in variant dynamics, there has also been significant changes in public attitudes and behaviors towards pandemic interventions, further complicating our understanding of how and why variants emerge. Understanding the driving factors behind viral evolution and competition has significant public health implications, yet it is unclear how in vitro estimates of variant competitiveness translate to real world selective advantages.

In Connecticut, the Delta variant emerged during a period of high variant competition and co-circulation and came to account for >99% of cases during the period of August - November 2021, only to be displaced by the Omicron BA.1 variant the following month[3]. Concurrent with these changes in variant dynamics, immunization rates in Connecticut have been steadily

increasing since the introduction of the vaccine in December of 2020, with over 80% of the state population having received at least two vaccine doses as of March 1, 2023[4]. While vaccinations are effective means of reducing the pool of susceptible individuals, the effectiveness of this transmission barrier is inversely related with a variant's ability to evade vaccine induced antibodies. Therefore, we hypothesize that in an increasingly vaccinated population, the emergence and continued fitness of SARS-CoV-2 variants over the course of the pandemic has been increasingly influenced by enhanced immune escape.

Various approaches have been implemented to understand the role of immune escape on determining variant fitness. Several studies have utilized mathematical models to simulate variant circulation in populations, however, these models make several assumptions that may not be generalizable to real-world populations[5-7]. Other studies have considered population level data during variant emergence periods stratified by various host factors, yet this focus on only select time periods limits our understanding of how determinants of variant fitness may have changed over the course of the pandemic[8-11]. Therefore, there is a need for a comprehensive analysis of variant dynamics in a fixed population setting across several periods of variant emergence, fixation, and displacement.

In this study we investigated the role of immune escape on SARS-CoV-2 variant competitiveness by combining sequencing data from the Yale SARS-CoV-2 genomic surveillance initiative with immunization records from the Yale New Haven Hospital system. By restricting our analyses to periods of variant emergence, we show that the emergence of the Omicron BA.1 variant may have been influenced by its increased ability to cause vaccine breakthrough infections relative to the dominant Delta variant, and that both age and sex are important factors in understanding variant competitiveness. By comparing variants to the pre-variant lineages over 18 months of the pandemic, we gained a better understanding of immune

escape as it relates to the ancestral virus from which the monovalent vaccine was constructed, and show, surprisingly, that the Alpha variant is associated with less immune escape than the pre-Alpha lineages. Overall, our study demonstrates the potential for combining genomic and clinical data to understand the drivers of pathogen evolution and provides a framework for understanding how in vitro evidence can be contextualized to population level effects in an extended outbreak setting.

Methods

Ethics statement

The Institutional Review Board from the Yale University Human Research Protection Program determined that the RT-qPCR testing and sequencing of de-identified remnant COVID-19 clinical samples obtained from clinical partners conducted in this study is not research involving human subjects (IRB Protocol ID: 2000028599).

Sample collection and Sequencing

SARS-CoV-2 positive clinical samples (nasal swabs in viral transport media) were collected via routine inpatient and outpatient testing by the Yale New Haven Hospital system and sent to the Yale SARS-CoV-2 Genomic Surveillance Initiative for further processing. Nucleic acid was extracted from 300µL of each clinical sample and eluted into 75µl of elution buffer using the MagMAX viral/pathogen nucleic acid isolation kit. The extracted nucleic acid was then tested for SARS-CoV-2 RNA via a “research use only” (RUO) RT-qPCR assay[12]. Samples with CT values ≤35 were then sequenced using the Illumina COVIDSeq Test RUO version to determine the viral lineage. Amplicons were then cleaned and pooled, and quantified using the Qubit High Sensitivity dsDNA kit. Negative controls were included in the RNA extraction, cDNA synthesis, and amplicon generation steps. Following quantification, the prepared libraries were sequenced

with a 2x150 approach on the Illumina NovaSeq at the Yale Center for Genomic Analysis, with each sample being given at least 1 million reads. As a part of the bioinformatics pipeline, reads were aligned to the Wuhan-Hu-1 reference genomes (GenBank MN908937.3) using BWA-MEM v.0.7.15[13] while adaptor sequences were trimmed, primer sequences were masked, and consensus genomes were called (simple majority >60% frequency) using iVar v1.3.133[14] and SAMtools[15]. An ambiguous 'N' was used when <20 reads were present at a site, and negative controls were confirmed to consist of ≥99% Ns. Finally, Pangolin v.2.4.2[16] was used to assign viral lineages[17].

Data cleaning

We selected 15,691 sequenced samples from the Yale SARS-CoV-2 Genomic Surveillance Initiative[3] for the period of January 1, 2021, to August 31,2022. We excluded any samples that were from non-Connecticut residents, those with missing unique identifiers, any samples with inadequate sequencing coverage to generate a Pangolin[18,19] lineage, and those with missing or inconsistent vaccination or date of birth data. For repeat infections, only the first record was retained while all subsequent infection records were excluded, resulting in a total sample size of 13,128. We then defined each sample by the number of vaccines received at least 14 days prior to the date of the sample collection and mapped the Pangolin Lineages to the WHO variants designations. Further details on the data exclusion criteria can be found in supplemental figure 1. All data cleaning steps were performed via the R statistical software[20].

Analysis 1: Vaccine Breakthrough Infections in Periods of Variant Emergence

To investigate factors associated with variant emergence, we first defined 4, 5-week intervals for time periods when a VOC was first emerging and displacing a previously established VOC in the population. These intervals capture the transition from the pre-Delta lineages to Delta, Delta

to Omicron BA.1, Omicron BA.1 to Omicron BA.2, and Omicron BA.2 to Omicron BA.4 and Omicron BA.5, respectively. We aggregated the pre-Delta lineages as well as Omicron BA. 4 and Omicron BA.5 variants into single categories in these analyses due to their sustained co-circulation in the population infection landscape (**Figure 1A**). We selected the date ranges for each of these 4, 5-week intervals to balance the number of unvaccinated cases attributable to each variant within each interval.

For each of the four study intervals, we then fitted a mixed effect multivariable logistic regression model with a dichotomous outcome variable for the two variants under comparison. For each of the models, the outcome reference level was set as the variant (or aggregated variant group) which emerged earlier in time. The primary predictor variable of interest was the number of vaccinations each individual had received by the time of infection, with 0 vaccinations as the reference level. This allowed us to estimate the odds of being infected with the emerging variant in each of the four periods of emergence, relative to the variant being displaced and number of immunizations received.

To control for potential confounding, we adjusted for several covariates and model structures and determined the best fit model via an Akaike information criterion (AIC) selection criteria (**Supplemental Document 1**). The covariates of the best fit model included: Number of vaccines stratified by waning immunity status, linear calendar time, sex, town of residence as a random effect variable, and age category (≤4, 5-17, 18-39, 40-64, ≥65). For the fixed effect covariates, we specified ≤4 years old and male as the reference levels for the age and sex, respectively. For each covariate we estimated an odds ratio from the fitted model along with 95% confidence intervals.

We then performed a sensitivity analysis on the interval durations to see if longer or shorter interval periods would affect our model results. To do this, we restricted our interval duration to 1 week, balanced the number of unvaccinated individuals for each variant in each of the four

time periods of variant emergence by changing the date range of the study interval, and ran each of the four regression models. We then repeated this process for interval durations of 3, 4, 6, 7, and 8 weeks, and compared the results of the model outputs (**Supplemental Document 1**). From this comparison we noted consistent effects across the majority of interval durations and selected 5 weeks as the optimal time frame to maximize study power while minimizing residual time effects.

Construction of the analysis model structure, covariates, and sensitivity analyses were done in accordance with WHO recommended methods[21].

Regression models were constructed in R statistical software and ran via the glmer package[20,22].

Analysis 2: Vaccine Breakthrough Infections Across Time Series

To compare the odds of vaccine breakthrough infections for all VOCs across the study period, we implemented a mixed effect multivariable ordinal logistic regression model for the escalating vaccination outcome categories of: unvaccinated (reference category), 1 dose >6 months since most recent vaccination at time of infection,1 dose ≤6 months since most recent vaccination at time of infection, 2 doses >6 months since most recent vaccination at time of infection, 2 doses ≤6 months since most recent vaccination at time of infection, 3 dose >6 months since most recent vaccination at time of infection, 3 doses ≤6 months since most recent vaccination at time of infection, 4 doses >6 months since most recent vaccination at time of infection, 4 doses ≤6 months since most recent vaccination at time of infection. The primary covariate of interest was the variant each individual in the study was infected with at the time of their sample collection, with the pre-Alpha lineages set as the reference group. This allowed us to estimate the odds of being a breakthrough case with higher levels of vaccination given the specific variant the individual presented with, relative to the pre-Alpha lineages. We chose the pre-Alpha lineages

as the reference level as these lineages would be the most antigenically similar to the ancestral virus from which the vaccine was derived, thereby allowing for a better understanding of the association between vaccinations and variant dynamics.

To control for potential confounding, we adjusted for several covariates including: Variant, patient age category (<18 years old, 18-65 years old, >65 years old), state-level vaccination coverage matched by age category and date of sample collection, dichotomous sex (male or female), town of residence as a random effect variable, and weekly calendar time as a continuous linear predictor (**Supplemental Table 1**). For the fixed effect covariates, we specified <18 years old and male as the reference levels for age and sex, respectively. To further account for confounding by time and potential residual autocorrelation, we included random effects for each calendar day of study, modeled using an autoregressive process of order one (i.e., AR1). For each covariate we estimated an odds ratio from the fitted model along with 95% confidence intervals.

To determine the effect of different waning immunity period definitions in our outcome variable levels, we performed a sensitivity analysis by changing the waning immunity durations from 6 months to 4 and 2 months and comparing the results of the three models (**Supplemental Table 1**). From this comparison we noted minimal differences between the three definitions of waning immunity and selected 6 months as the optimal model.

State-level vaccination data were sourced from the CDC COVID Data Tracker database and matched to each datapoint by age group and the date of the sample collection[23].

The models were constructed in SAS statistical software, Version 9.4 of the SAS System and fit using Proc Glimmix. Copyright © SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.

Results

Emergence of Variants in a Vaccinated Population

To investigate the role immune escape has on variant fitness in a population setting, we matched sequencing data to clinical metadata for 13,128 laboratory confirmed SARS-CoV-2 infections from Connecticut residents for the period of February 3, 2021, to August 31, 2022. While representing only a portion of all statewide cases, our study sample shows comparable variant trends to those of the state level and spans a sufficient length of time to capture the emergence and displacement of several variants of concern (**Figure 1A & B**). For this period of time there are notable increases in vaccine uptake rates, yet these increases in vaccination rates are not matched by decreasing case counts (**Figure 1C**). Underlying these changes in vaccination rates, variant trends, and raw case counts, we also see an increasing number of vaccine breakthrough infections amongst individuals with increasing vaccine doses across the study period (**Figure 1D**). Therefore, while this study sample is broadly representative of state level population dynamics, it is not clear how vaccination uptake rates and vaccine breakthrough infections are influencing the observed variant trends.

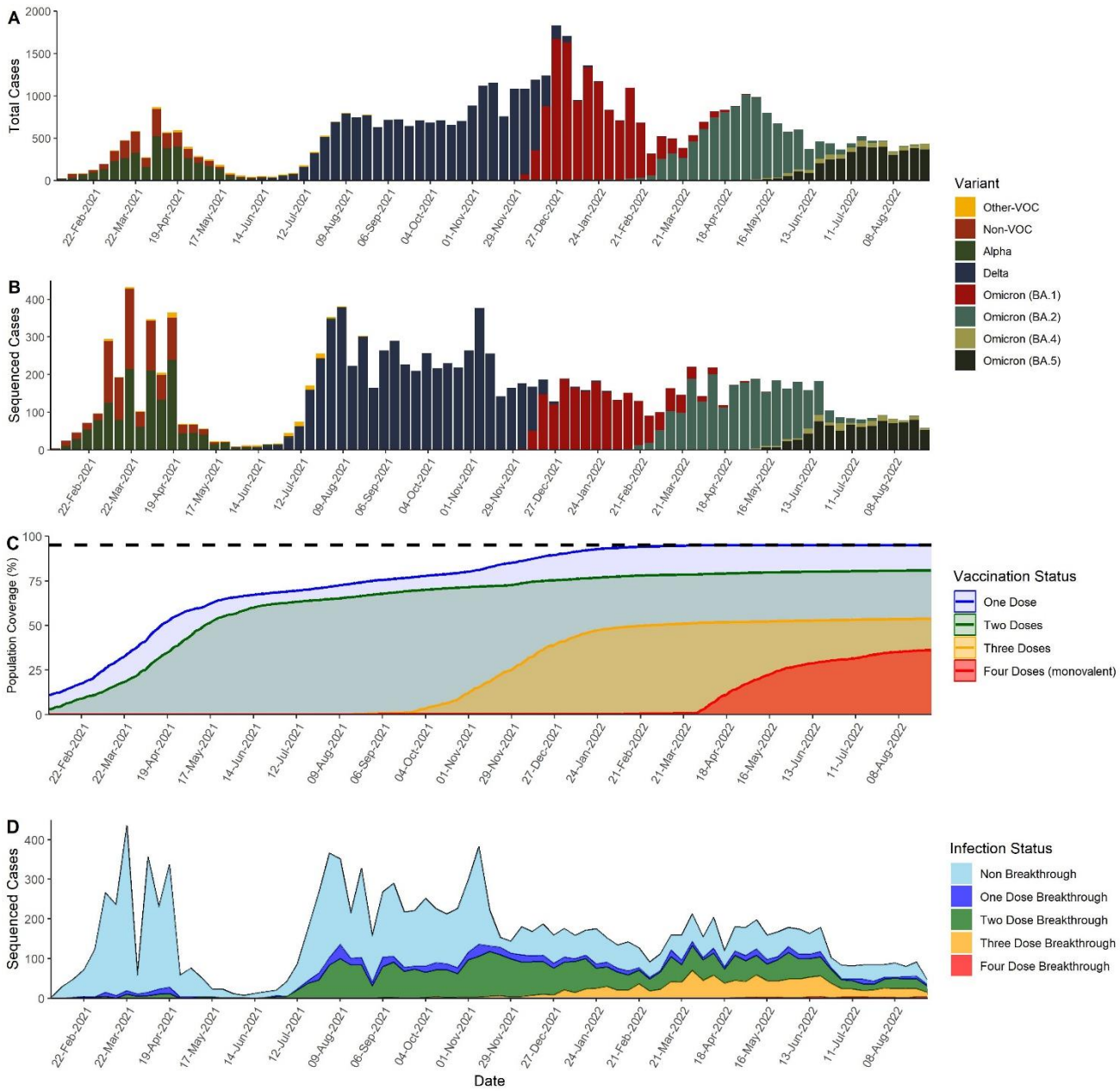

Figure 1. SARS-CoV-2 variant and vaccination trends. A. Weekly SARS-CoV-2 major VOC trends amongst Connecticut residents from February 3, 2021, to August 31, 2022. Data retrieved from COVIDTrackerCT (https://covidtrackerct.com/). **B.** Weekly SARS-CoV-2 major VOC trends amongst the study population from February 3, 2021, to August 31, 2022. **C.** Weekly vaccination coverage rates amongst Connecticut residents by number monovalent vaccine doses from February 3, 2021, to August 31, 2022. Data retrieved from the CDC COVID-19 dashboard (covid.cdc.gov/covid-data-tracker). **D.** Weekly COVID-19 vaccine breakthrough infections amongst the study population by number of monovalent doses received prior to infection from February 3, 2021, to August 31, 2022.

Vaccine Breakthrough Infections in Periods of Variant Emergence

To investigate the role of immune escape in periods of variant emergence, we restricted our analyses to 4, 5-week long periods of variant co-circulation and fitted a mixed effect multivariable logistic regression model for each 5-week time interval to determine the odds of infection with the emerging variant relative to the established variant and the number of vaccine doses received (**Figure 2**). Due to the antigenic distinctiveness of the Omicron variant sublineages, we chose to analyze the BA.1 and BA.2 lineages independently while examining the BA.4 and BA.5 lineages together due to their contemporaneous co-circulation in the population[24,25]. To determine the effect of the interval durations on the model results, we performed a sensitivity analysis by comparing the model outputs for 6 different interval lengths and found minimal differences in the results (**Supplemental Document 1**). While the monovalent vaccine is effective against Covid-19 infections, the protection granted from immunizations decreases with the amount of time since the vaccine was administered due to waning of circulating neutralizing antibodies[26-29]. Therefore, to account for waning immunity, we stratified the vaccination status variable on the condition of the sample collection date being within or outside of a 5-month window since the most recent prior immunization.

Our study population has a broad representation across age groups, variant lineages, and vaccination statuses at time of infection (**Tables 1 & 2**). However, due to the time frame of our study and sample collection methods, there is limited representation of individuals with 4 vaccination doses and of variants that did not account for a large proportion of population level infections.

Table 1: Patient demographics by vaccination status† (n = 13128)

	Unvaccinated (n=7549)	1 dose (n=824)	2 doses (n=3498)	3 doses (n=1208)	4 doses‡ (n=49)
Age group, No. (%)⁑					
<2	271 (3.6)	0 (0)	1 (0.0)	0 (0)	0 (0)
2-4	513 (6.8)	0 (0)	0 (0)	0 (0)	0 (0)
5-11	1195 (15.8)	21 (2.5)	86 (2.5)	0 (0)	0 (0)
12-17	760 (10.1)	21 (2.5)	184 (5.3)	14 (1.2)	0 (0)
18-24	734 (9.7)	52 (6.3)	192 (5.5)	43 (3.6)	0 (0)
25-39	1746 (23.1)	227 (27.5)	859 (24.6)	268 (22.2)	0 (0)
40-49	893 (11.8)	146 (17.7)	597 (17.1)	199 (16.5)	3 (6.1)
50-64	976 (12.9)	252 (30.6)	900 (25.7)	369 (30.5)	13 (26.5)
65-74	287 (3.8)	62 (7.5)	403 (11.5)	172 (14.2)	21 (42.9)
≥75	174 (2.3)	43 (5.2)	276 (7.9)	143 (11.8)	12 (24.5)
Sex, No. (%)⁋					
Female	3356 (44.5)	388 (47.1)	1809 (51.7)	541 (44.8)	5 (10.2)
Male	3273 (43.4)	342 (41.5)	1366 (39.1)	361 (29.9)	8 (16.3)
Other	16 (0.2)	0 (0.0)	3 (0.1)	1 (0.1)	0 (0.0)
Unknown	904 (12.0)	94 (11.4)	320 (9.1)	305 (25.2)	36 (73.5)

† As determined by the number of vaccinations received ≥14 days from the sample collection date
‡ Defined as having received 4 doses of the monovalent vaccine. Individuals who received the bivalent vaccine as their 4th dose were not included due to the timeframe of this study.
⁋ For all analyses, only those in the "Female" and "Male" categories were considered
⁑ Individuals of unknown age were removed as a part of the data exclusion criteria (supplemental figure 1)

Table 2: Variant frequencies by vaccination and waning immunity status[†]

(n = 13128)

	0 Doses (n=7549)	1 Dose ≥6 MTHs (n=441)	1 Dose <6 MTHs (n=383)	2 doses ≥6 MTHs (n=2442)	2 doses <6 MTHs (n=1056)	3 doses ≥6 MTHs (n=451)	3 doses <6 MTHs (n=757)	4 doses[‡] (n=49)	Total (n=13128)
Variant, No. (%)[⁑]									
Unnamed[⁋]	300 (4.0)	0 (0.0)	12 (3.1)	0 (0.0)	10 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	322 (2.5)
Alpha	1355 (17.9)	0 (0.0)	41 (10.7)	0 (0.0)	32 (3.0)	0 (0.0)	0 (0.0)	0 (0.0)	1428 (10.9)
Beta	7 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	8 (0.1)
Delta	3268 (43.3)	177 (40.1)	206 (53.8)	943 (38.6)	775 (73.4)	0 (0.0)	38 (5.0)	0 (0.0)	5407 (41.2)
Epsilon	27 (0.4)	0 (0.0)	3 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	30 (0.2)
Eta	3 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.0)
Gamma	47 (0.6)	0 (0.0)	3 (0.8)	0 (0.0)	3 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	53 (0.4)
Iota	580 (7.7)	0 (0.0)	26 (6.8)	0 (0.0)	19 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	625 (4.8)
Kappa	2 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.0)
Lambda	2 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.0)
Mu	32 (0.4)	0 (0.0)	3 (0.8)	0 (0.0)	13 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	48 (0.4)
BA.1	767 (10.2)	79 (17.9)	40 (10.4)	610 (25.0)	102 (9.7)	5 (1.1)	271 (35.8)	0 (0.0)	1874 (14.3)
BA.2	797 (10.6)	122 (27.7)	44 (11.5)	636 (26.0)	88 (8.3)	217 (48.1)	406 (53.6)	19 (38.8)	2329 (17.7)
BA.4	65 (0.9)	11 (2.5)	2 (0.5)	25 (1.0)	3 (0.3)	35 (7.8)	6 (0.8)	5 (10.2)	152 (1.2)
BA.5	296 (3.9)	52 (11.8)	2 (0.5)	226 (9.3)	10 (0.9)	194 (43.0)	36 (4.8)	25 (51.0)	841 (6.4)
Recombinant	1 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.0)

†Waning immunity status is defined as being <6 or ≥6 months from the most recent prior vaccination

‡ Defined as having received 4 doses of the monovalent vaccine. Individuals who received the bivalent vaccine as their 4th dose were not included due to the timeframe of this study.

⁋ Unnamed include all lineages that occurred prior to the Alpha variant, following Pangolin lineage naming conventions[18]

⁑ Variants that have n≤10 are excluded for all analyses. These include the Beta, Eta, Kappa, Lambda, and Recombinant variants.

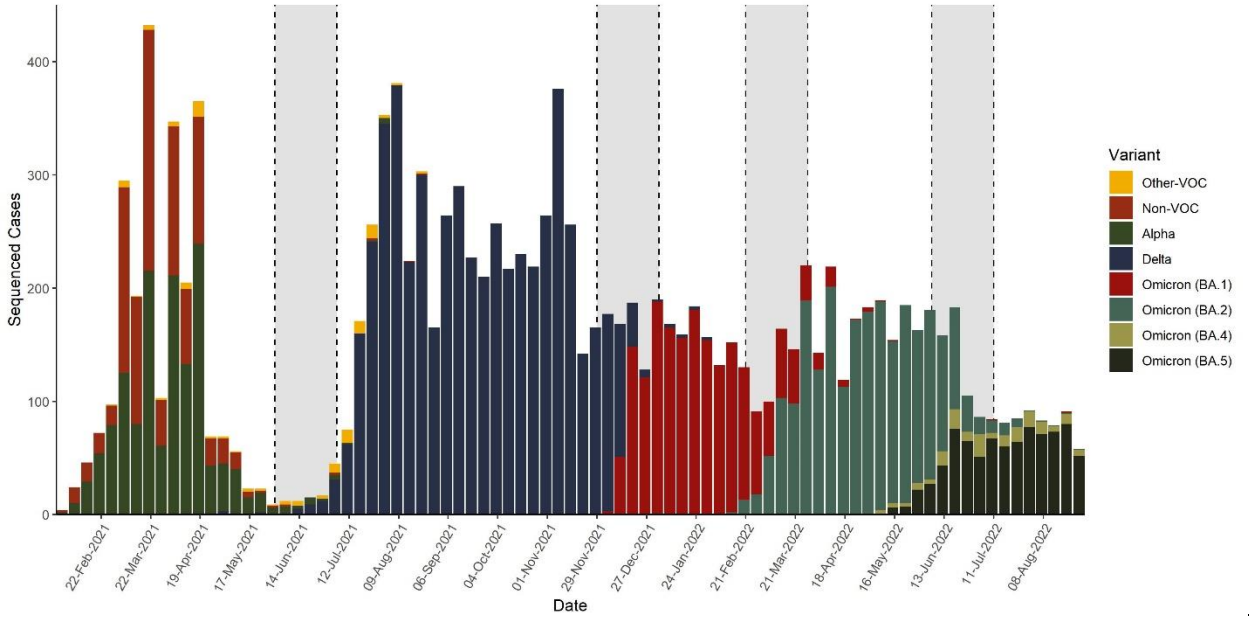

Figure 2. Periods of variant emergence. Weekly variant trends over the study period (February 3, 2021 - August 31, 2022) separated into 4, 5-week periods (denoted with grey boxes) when one variant is emerging in the population and displacing a previously established variant. These four periods correspond to the emergence of the Delta, Omicron BA.1, Omicron BA.2, and Omicron BA.4 and BA.5 variants, respectively, for the respective time periods of 2021-06-03 – 2021-07-08, 2021-11-30 – 2022-01-04, 2022-02-23 – 2022-03-30, 2022-06-09 – 2022-07-14.

No Effects of Vaccine Breakthrough Infections on Delta Emergence

To investigate the emergence of the Delta variant, we identified an emergence period of June 3, 2021, to July 8, 2021. To account for the reduced sequencing capacity for this period and lack of a clearly dominant variant in the population, we aggregated all pre-Delta lineages as the variant reference group. Aggregating the pre-Delta lineages further allowed us to understand what factors enabled Delta to emerge in a population of high variant diversity and competition. For this period of emergence, we see approximately equal representation of the pre-Delta lineages to the Delta variant (**Supplemental Table 2**), however, we also see relatively few

vaccine breakthrough infections, likely as a result of the limited vaccine uptake for this time period of the pandemic (**Figure 3A, Table 1**). Due to the lack of 1-dose vaccine breakthrough infections in this emergence period, we were unable to generate reliable estimates for the effect of these vaccination categories on the odds of being infected with the Delta variant.

After controlling for time, age, and sex, we did not find any significant effects of vaccinations on the odds of being infected with the Delta variant relative to the pre-Delta lineages (**Figure 3B, Supplemental Table 3**). These findings suggest that the emergence of the Delta variant may not have been associated with an enhanced ability to cause infections in vaccinated individuals and could have instead been due to other factors associated with variant fitness, such as increased intrinsic transmissibility.

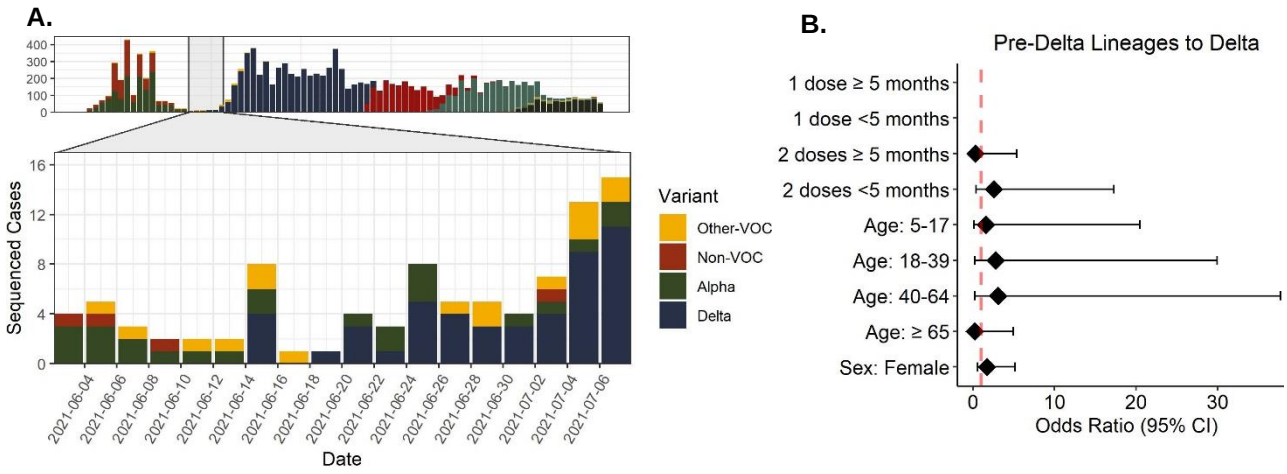

Figure 3. Emergence of Delta Variant. A. 5-week emergence period of the Delta variant from the pre-Delta lineages (June 3, 2021 - July 8, 2021) in the context of the full time series. Variant counts are aggregated to 2-day periods. Variant counts by vaccination status are available in supplemental table 2. **B.** Odds of being infected with the Delta variant by vaccination status (reference: unvaccinated), age (reference: <5), and sex (reference: male), relative to the pre-Delta lineages. An OR>1 indicates a greater odds of being infected with the Delta variant than the pre-Delta lineages. Regression ORs and p-values are available in supplemental table 3.

Increased Odds of Vaccine Breakthrough Infections with Omicron BA.1

Having found no effects of vaccinations on the emergence of the Delta variant, we identified an emergence period of November 30, 2021, to January 4, 2022, to investigate the emergence of the Omicron BA.1 variant. For this period of emergence, we note an increased number of vaccine breakthrough infections with increasing vaccine doses in both variants relative to the emergence period of the Delta variant (**Figure 4A, Supplemental Table 4**). The comparative underrepresentation of the <5 month dose category to the ≥5 month dose category in both variants is likely due to the timing of this study period relative to when first and second vaccine doses were first made widely available in the state[30]. After controlling for time, age, and sex, we identified significantly increased odds of being infected with the Omicron BA.1 variant relative to the Delta variant for those with 2 vaccine doses ≥5 months [**OR**: 2.093, **95% CI:** 1.11, 3.94] and those with 3 vaccine doses ≤5 months [**OR**: 7.118, **95% CI:** 1.44, 35.17] (**Figure 4B, Supplemental Table 5**). We did not identify any significant effects of age or sex on the odds of being infected with the Omicron BA.1 variant relative to the Delta variant.

These findings suggest that the emergence of the Omicron BA.1 variant over the Delta variant may be partly attributable to its enhanced immune escape and ability to cause infections amongst vaccinated individuals.

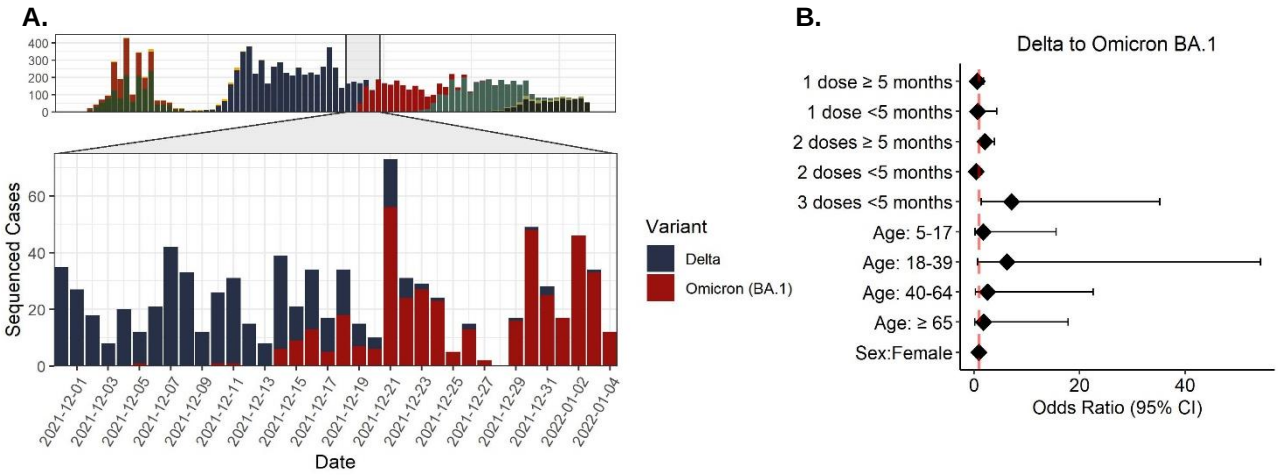

Figure 4. Emergence of Omicron BA.1 variant. A. 5-week emergence period of the Omicron BA.1 variant from the Delta variant (November 30, 2021 - January 4, 2022) in the context of the full time series. The expanded variants trends are displayed as daily counts. Variant counts by vaccination status are available in supplemental table 4. **B.** Odds of being infected with the Omicron BA.1 variant by vaccination status (reference: unvaccinated), age (reference: <5), and sex (reference: male), relative to the Delta variant. An OR>1 indicates a greater odds of being infected with the Omicron BA.1 variant than the Delta variant. Regression ORs and p-values are available in supplemental table 5.

No Effects of Vaccine Breakthrough Infections on Omicron BA.2 Emergence

Having found evidence for a significant effect of vaccinations on the emergence of the Omicron BA.1 variant, we identified an emergence period of February 23, 2022, to March 30, 2022, to investigate the emergence of the Omicron BA.2 variant. For this period, we note comparable representation of the vaccine categories for both variants as well as a more gradual emergence of the Omicron BA.2 variant in comparison to the previous emergences of the Delta and Omicron BA.1 variants (**Figure 5A, Supplemental Table 6**). This more gradual displacement of the circulating variant could suggest the fitness advantage of the BA.2 variant over the BA.1 variant is less significant than that of the previous variants.

After controlling for time, age, and sex, we did not identify any significant effects of vaccinations on the odds of being infected with the Omicron BA.2 variant relative to the Omicron BA.1 variant

(**Figure 5B**). We did identify a significantly increased risk of being infected with the emerging variant with increasing age [**Age 5-17 OR**: 4.587, **95% CI:** 1.35, 15.59 | **Age 18-39 OR**: 4.038, **95% CI:** 1.25, 13.04 | **Age 40-64 OR**: 4.068, **95% CI:** 1.26, 13.12 | **Age 65+ OR**: 5.266, **95% CI:** 1.49, 18.60] (**Supplemental Table 7**). These findings suggest that the emergence of the Omicron BA.2 variant may not have been associated with an enhanced ability to cause infections in vaccinated individuals, but may have been influenced by biological or behavioral differences associated with age.

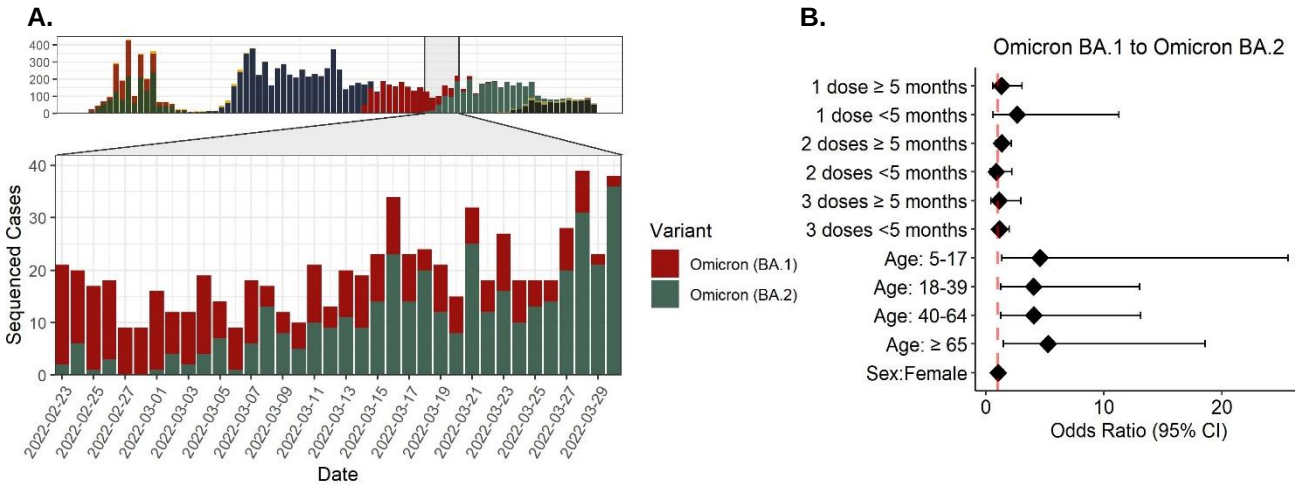

Figure 5. Emergence of Omicron BA.2 variant. A. 5-week emergence period of the Omicron BA.2 variant from the Omicron BA.1 variant (February 23, 2022 - March 30, 2022) in the context of the full time series. The expanded variants trends are displayed as daily counts. Variant counts by vaccination status are available in supplemental table 6. **B.** Odds of being infected with the Omicron BA.2 variant by vaccination status (reference: unvaccinated), age (reference: <5), and sex (reference: male), relative to the Omicron BA.1 variant. An OR>1 indicates a greater odds of being infected with the Omicron BA.2 variant than the Omicron BA.1 variant. Regression ORs and p-values are available in supplemental table 7.

Increased Odds of Vaccine Breakthrough Infections with Omicron BA.4 and BA.5

Having found significant effects of age but no effects of vaccinations on the emergence of the Omicron BA.2 variant, we identified a timeframe of June 9, 2022, to July 14, 2022, to investigate

the emergence of the Omicron BA.4 and BA.5 variants. Due to the limited representation of the <5 month vaccine categories relative to the ≥5 month categories, likely due to the timing of this emergence period relative to vaccine eligibility dates, we aggregated these categories to reflect the number of vaccine doses regardless of waning immunity status (**Figure 6A, Supplemental Table 8**). Additionally, we removed the sex parameter of the model due to a lack of information on sex for individuals in this time period.

After controlling for time and age, we identified significantly increased odds of being infected with the Omicron BA.4 and BA.5 variants relative to the Omicron BA.2 variant for those with 3 vaccine doses [**OR**: 1.66, **95% CI:**1.01, 2.73] (**Figure 6B, Supplemental Table 9)**. The large variance seen in the 4-dose effect estimate is likely due to the limited number of 4-dose vaccine breakthrough infections for this time period, thereby limiting our ability to properly assess this effect. We did not identify any significant effects of age on the odds of being infected with the Omicron BA.4 and BA.5 variants after controlling for the number of vaccinations.

These findings suggest that the emergence of the Omicron BA.4 and BA.5 variants over the Omicron BA.2 variant may have been partly influenced by their ability to cause infections amongst highly vaccinated individuals.

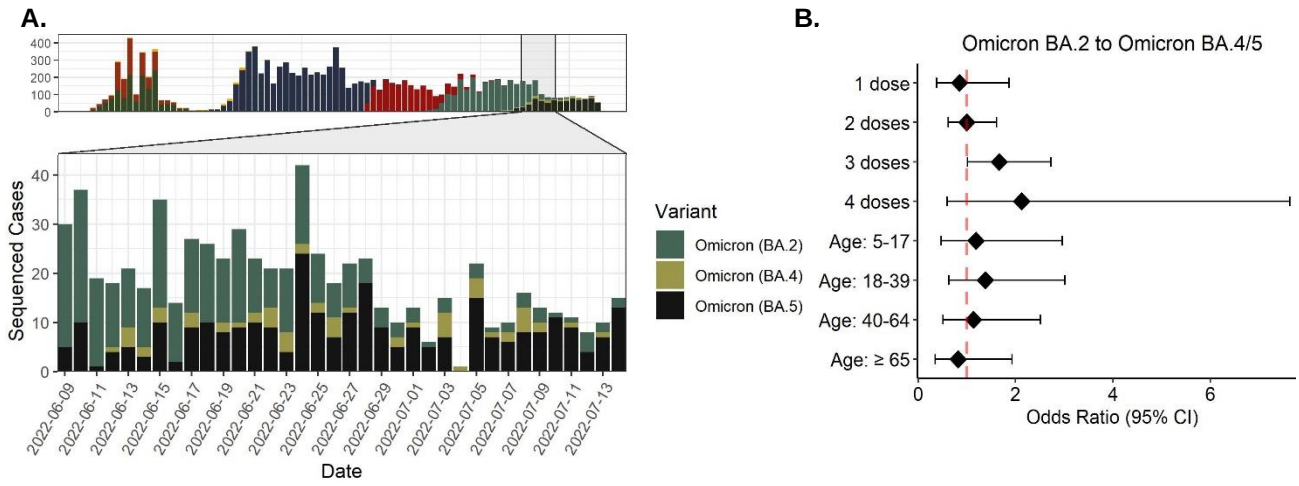

Figure 6. Emergence of Omicron BA.4/5 variant. A. 5-week emergence period of the Omicron BA.4/5 variant from the Omicron BA.2 variant (June 9, 2022 - July 14, 2022) in the context of the full time series. The expanded variants trends are displayed as daily counts. Variant counts by vaccination status are available in supplemental table 8. **B.** Odds of being infected with the Omicron BA.4/5 variant by vaccination status (reference: unvaccinated), age (reference: <5), and sex (reference: male), relative to the Omicron BA.2 variant. An OR>1 indicates a greater odds of being infected with the Omicron BA.4/5 variant than the Omicron BA.2 variant. Regression ORs and p-values are available in supplemental tables 9 and 10.

Vaccine Breakthrough Infections Across Time Series

Having shown that vaccine breakthrough infections may have played an important role in the emergence of the Omicron BA.1 variant, and to a lesser degree the emergence of the Omicron BA.4 and BA.5 variants, we wanted to further investigate the role of vaccine breakthrough infections on variant fitness across the entirety of the study period. To accomplish this, we fitted a mixed effect multivariable logistic regression model to our full study population. To account for changes in vaccination eligibility dates by age group, we matched each individual by their age group and collection date to a state-wide vaccination coverage database.

To account for waning immunity, we stratified our model outcome variable levels on the condition of the sample collection date being within or outside of a 6-month window since the

most recent prior immunization. Finally, to account for any residual correlations, we included random effects for each calendar day of study, modeled using an autoregressive process of order one (**Supplemental Figure 4**).

Decreased Odds of Vaccine Breakthrough Infections with Alpha Variant

After adjusting for calendar time, sex, age, location, and population level vaccination coverage by age group, we found significantly decreased odds of being a more vaccinated breakthrough case amongst those infected with the Alpha variant relative to the pre-variant lineages [**OR**: 0.474, **95% CI:** 0.26, 0.88] (**Figure 7, Table 3**). We did not find other significant associations between any variants and the odds of being a more vaccinated breakthrough case, however, we found a strong protective effect associated with female sex [**OR**: 0.796, **95% CI:** 0.73,0.86] as well as a positive association between increasing age category and odds of being a vaccine breakthrough infection [**Age 18-64 OR**: 2.33, **95% CI:** 1.95, 2.79 | **Age 65+ OR**: 3.32, **95% CI:** 2.64, 4.19].

In our model we defined waning immunity in our outcome variable as being within or outside a 6-month period from the most recent vaccination to the time of infection, however, this period of waning immunity can be highly variable and is influenced by several factors including an individual's age, number of previous vaccinations, comorbidities, as well as exposure to previous variants[31-37]. Therefore, to test the sensitivity of our results to our definition of a 6-month waning immunity period, we tested our model with a 4-month and 2-month waning immunity period, and did not find significant differences in the results of the three models indicating our results are not sensitive to changes in this parameter (**Supplemental Table 1**).

These results indicate that, with the exception of the Alpha variant, immune escape may not have played a significant role in variant fitness throughout the pandemic. In the case of the

Alpha variant, these findings suggest that the lack of immune escape associated with the variant may have contributed to its inability to completely outcompete the other co-circulating variants. These results are surprising given in vitro evidence for comparable immune escape between the Alpha variant and the pre-Alpha lineages[38-40].

In addition to variant effects, we found significant effects of both age and sex, with increasing age being associated with increased odds of vaccine breakthrough infections and female sex associated with decreased odds of vaccine breakthrough infections. These results suggest there may be biological or behavioral differences between age and sex groups that influence the likelihood of being a vaccine breakthrough infection. Taken together, these results suggest that individual demographics may be more influential in determining the odds of being a vaccine breakthrough infection than the circulating variant.

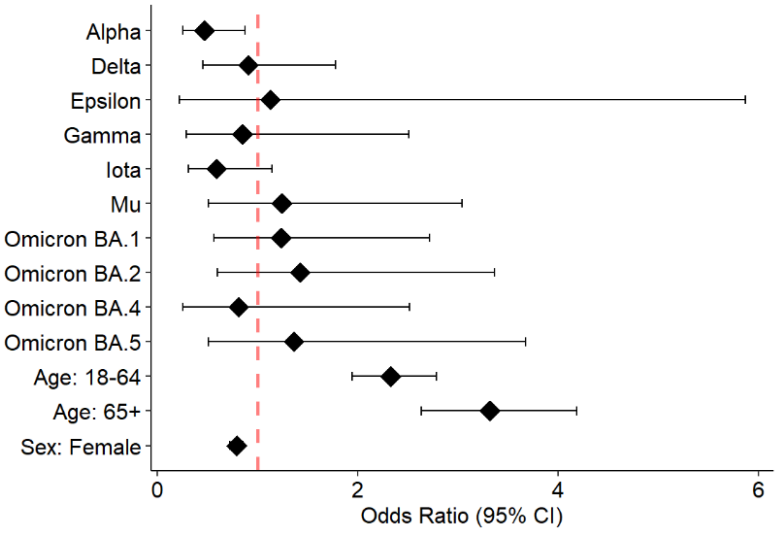

Table 3: Analysis 2 Results

Covariates	OR (95% CI)	p-value
Variant		
Unnamed	Ref.	Ref.
Alpha	0.474 (0.26, 0.88)	0.019
Delta	0.910 (0.46, 1.78)	0.784
Epsilon	1.134 (0.22, 5.87)	0.881
Gamma	0.854 (0.29, 2.51)	0.775
Iota	0.594 (0.31, 1.15)	0.120
Mu	1.246 (0.51, 3.04)	0.630
Omicron BA.1	1.240 (0.57, 2.72)	0.591
Omicron BA.2	1.428 (0.60, 3.37)	0.416
Omicron BA.4	0.816 (0.26, 2.52)	0.724
Omicron BA.5	1.369 (0.51, 3.68)	0.534
Age category		
<18	Ref.	Ref.
18-64	2.330 (1.95, 2.79)	<.0001
65+	3.322 (2.64, 4.19)	<.0001
Vaccination Coverage	3.171 (2.81, 3.57)	<.0001
Sex		
Male	Ref.	Ref.
Female	0.796 (0.73, 0.86)	<.0001
Time	1.359 (1.08, 1.71)	0.009

Figure 7. Odds of vaccine breakthrough infections by variant and patient demographics. Odds of having received ≥1 vaccine dose prior to infection with SARS-CoV-2 by variant (reference: unnamed lineages), age (reference: <18 years olds), and sex (reference: male) amongst the study population (n=13,128) over the period of February 3, 2021, to August 31, 2022. ORs >1 indicate an increased odds of being a vaccine breakthrough infection relative to the reference group of unnamed lineages. Data are shown as means with 95% confidence intervals. ORs and p-values can be found in Table 3.

Discussion

Here we investigated whether any of the SARS-CoV-2 variants of concern were associated with an increased odds of vaccine breakthrough infections in a population of Connecticut residents. We aimed to determine if in vitro findings of immune escape translate to variant fitness in a population setting and to better understand the role of immune escape on variant emergence. By fitting multivariable regression models across our full study time series and in periods of variant emergence, we show that the Alpha and Omicron BA.1 variants are associated with a decreased likelihood of inducing an infection in vaccinated individuals and an increased likelihood of being present in a vaccine breakthrough infection, respectively. We further show strong associations between age and sex with the odds of being a vaccine breakthrough

infection as well as a positive association between increasing age and the odds of being infected with the Omicron BA.2 variant. To test the validity of these findings, we performed several sensitivity analyses and found our results to be robust to changes in our model structures and assumptions.

Our findings suggest that immune evasiveness may have been an important factor in the emergence of the Omicron BA.1 variant and that in vitro determinations of variant fitness may be reflective of variant competitiveness in population settings. Indeed, several studies have found that the Omicron BA.1 variant was significantly more capable of inducing vaccine breakthrough infections than any previous variant[11, 41-44]. In a population where most of the members have natural, vaccine-induced, or hybrid immunity, such as that seen in Connecticut during the latter months of the Delta variant, a variant with high immune evasiveness would have access to a larger pool of susceptibles than a variant with low immune evasiveness, thereby giving it a selective advantage. This concept was shown in a population-based study looking solely at the emergence of the Omicron BA.1 variant in New England, which similarly showed higher odds of being infected with the BA.1 variant over the Delta variant among vaccinated individuals[45].

However, this selective advantage likely only applies when the emerging variant has greater immune escape than the variant being replaced, as variants of comparably high immune evasiveness would be drawing from the same pool of vaccinated yet still susceptible individuals. This may explain why immune escape did not seem to play a factor in the emergence of the Omicron BA.2 variant over the Omicron BA.1 variant, as these variants have comparable levels of immune evasiveness[9,40,41]. Similarly, the Omicron BA.4 and BA.5 variants both possess only a slightly increased immune evasiveness over the Omicron BA.2 variant, which could explain why there was only an increased likelihood of being infected with the BA.4 and 5 variants over

the BA.2 variant amongst those with three vaccine doses[46-49]. Due to the timing of this study period, we had relatively few individuals with four vaccinations, and thus it is unclear if the immune escape advantage seen in the Omicron BA.4 and BA.5 variants amongst those with three doses would also be seen amongst those with four doses.

In a population where immunity is low, the selective advantage of immune escape would be far less pronounced than that granted by increased intrinsic transmissibility. This likely explains the rise of the Delta variant, which emerged in a period of low population level immunity and which in vitro studies have shown to be associated with moderate immune escape but significantly increased intrinsic transmissibility[50-53]. Indeed, a population-based study in New England attributed the rise of the Delta variant largely to its intrinsic transmissibility, further highlighting the importance of understanding population characteristics as determinants of variant fitness[54].

In comparing the odds of vaccine breakthrough infections across all the variants in our study, we sought to understand if immune escape plays an important role not only in the emergence of a variant, but also in its sustained circulation. Doing so, we found that the only variant significantly associated with vaccine breakthrough infections is the Alpha variant, and that this association was such that being infected with this variant decreased the odds of being a breakthrough infection. This result is surprising given that in vitro studies have found the Alpha variant to have comparable, if not slightly increased, immune evasiveness to the pre-Alpha lineages[38-40]. One reason for this could be the relatively low representation of vaccinated individuals infected with the Alpha variant in the model due to the low overall population infection rates (**Table 2** & **Figure 1A**) combined with the low population vaccination rates (**Table 1**) for this early part of the pandemic. Alternatively, this could indicate that in-vitro estimates of immune escape for the Alpha variant are not an appropriate proxy for the ability of the variant to induce vaccine breakthrough infections in population settings.

Additionally, it is surprising that the Omicron BA.1 variant, which was found to be highly associated with vaccine breakthrough infections in the pairwise comparison to the Delta variant, is not significant in this model. This could indicate that, while immune escape played an important role in the emergence of the BA.1 variant, this selective advantage may have been less pronounced after this period of initial emergence.

The significant age and sex effects seen in both models may have been influenced by differences in biological and behavioral risk factors. Indeed, increasing age is correlated with reduced immune function and therefore increased susceptibility to infection after vaccination[34-37], which could explain the significantly increased risk of vaccine breakthrough infections in older age groups seen in analysis 2. The reason why we see increased risk of being infected with the Omicron BA.2 variant relative to the Omicron BA.1 variant amongst older age groups in analysis 1 is less clear; however, this association could be influenced by changes in test seeking behaviors or residual confounding. Similarly to age, several factors could be influencing the significant effects of sex seen on the odds of being a vaccine breakthrough infection. In Connecticut, females have had consistently higher rates of vaccine uptake throughout the pandemic, while nationally males have lower reported case rates and higher mortality rates[55,56]. Additionally, sex plays an important role in determining the strength and duration of immune responses to vaccinations and natural infections, and several studies have found sex to be an important effect modifier in disease pathogenesis[57-61]. Therefore, further research is needed to understand how sex influences the risk of being a vaccine breakthrough infection in a population setting.

This study had several limitations. Firstly, we did not have information on previous infections that may have occurred outside the YNHH system. While known reinfections were excluded, we did not have access to information on tests that may have occurred in other settings, such as at-

home testing, that would have allowed for further analyses into the effects of hybrid immunity on variant dynamics. Secondly, adjusting for calendar time presented a notable challenge in this study. Over the course of this study period, there were several changes to vaccination coverage rates, incidence rates, health behaviors, and public health policy that may have impacted the variant landscape. By adjusting for time in our regression models and incorporating autoregressive random effects, we reduced the risk for confounding due to time, however, residual confounding may still be present. Thirdly, underrepresentation of covariate categories necessitated modifications to some of the analysis models. Namely, the lack of individuals with vaccinations within 5 months of their infection date in the Omicron BA.4 and BA.5 emergence period necessitated aggregating the vaccination covariate categories by dose regardless of timing. Additionally, the lack of recorded sex amongst individuals in the fourth date interval necessitated removing the sex covariate from this model. Given that the results of the Omicron BA.4 and BA.5 emergence analysis did not change substantially before and after aggregating the vaccination status covariate (**Supplemental Tables 9 & 10**) and given the lack of sex effects seen in the other variant emergence analyses, we do not believe these changes meaningfully impacted the results. Fourthly, we were not able to adjust for race/ethnicity, vaccine manufacturer, or reasons for testing due to limitations in our data. While this may limit the generalizability of our findings, we feel that the large sample size and catchment area of our study population reduces the potential for bias. Finally, the sample size of the analyses was limited on account of both natural population infection dynamics as well as changing sequencing capacities. Notably, the co-circulation of several variants early in the study period combined with a limited sequencing capacity resulted in limited representation of these variants in the study sample relative to later variants. Despite this, we show that the variant dynamics in our study population reflect those of the wider state (**Figure 1A & B**) and we retained sufficient statistical power to draw inferences from the data.

Conclusions

Vaccinations are a safe and effective means of preventing infections and slowing the spread of outbreaks, yet their effects on pathogen dynamics and evolution should not be overlooked. Understanding how and why pathogens change over the course of an outbreak and in response to variation in the immunity landscape has far reaching implications for public health policy and practice. Future applications could see this approach used with other pathogens or with real-time data to better understand how pathogen diversity and selective pressures change in response to an actively evolving population immunity landscape.

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Supplemental Table 1: Analysis 2 Model Comparison and Sensitivity Analysis

	Random Effects Only						Random Effects & Time Trend Adjustment						Random Effects & Time Trend Adjustment & Vaccination Coverage by Age and Date					
	2-month waning immunity		4-month waning immunity		6-month waning immunity		2-month waning immunity		4-month waning immunity		6-month waning immunity		2-month waning immunity		4-month waning immunity		6-month waning immunity	
Covariates	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
Sex																		
Male	Ref.		Ref.		Ref.		Ref.		Ref.		Ref.		Ref.		Ref.		Ref.	
Female	0.789 (0.73, 0.86)	<.0001	0.798 (0.74, 0.87)	<.0001	0.807 (0.74, 0.87)	<.0001	0.788 (0.73, 0.86)	<.0001	0.797 (0.73, 0.86)	<.0001	0.807 (0.74, 0.87)	<.0001	0.778 (0.72, 0.85)	<.0001	0.787 (0.72, 0.85)	<.0001	0.796 (0.73, 0.86)	<.0001
Time	-	-	-	-	-	-	2.181 (1.68, 2.83)	<.0001	2.094 (1.62, 2.71)	<.0001	1.860 (1.46, 2.37)	<.0001	1.570 (1.22, 2.02)	0.0005	1.468 (1.15, 1.87)	0.002	1.359 (1.08, 1.71)	0.0088
Vaccination Coverage	-	-	-	-	-	-	-	-	-	-	-	-	3.111 (2.76, 3.51)	<.0001	3.106 (2.76, 3.50)	<.0001	3.171 (2.81, 3.57)	<.0001
Age																		
<18	Ref.		Ref.		Ref.		Ref.		Ref.		Ref.		Ref.		Ref.		Ref.	
18-64	10.777 (9.36, 12.41)	<.0001	9.970 (8.67, 11.46)	<.0001	9.256 (8.06, 10.62)	<.0001	10.807 (9.38, 12.45)	<.0001	9.930 (8.64, 11.41)	<.0001	9.284 (8.09, 10.66)	<.0001	2.821 (2.35, 3.39)	<.0001	2.587 (2.16, 3.10)	<.0001	2.330 (1.95, 2.79)	<.0001
65+	25.659 (21.61, 30.47)	<.0001	21.315 (18.02, 25.22)	<.0001	19.717 (16.70, 23.28)	<.0001	25.616 (21.56, 30.43)	<.0001	21.151 (17.88, 25.02)	<.0001	19.709 (16.69, 23.28)	<.0001	4.500 (3.55, 5.70)	<.0001	3.731 (2.95, 4.71)	<.0001	3.322 (2.64, 4.19)	<.0001
Variant																		
Unnamed	Ref.		Ref.		Ref.		Ref.		Ref.		Ref.		Ref.		Ref.		Ref.	
Alpha	0.676 (0.35, 1.29)	0.2363	0.665 (0.35, 1.27)	0.215	0.651 (0.34, 1.23)	0.1884	0.602 (0.32, 1.12)	0.1107	0.594 (0.32, 1.10)	0.0987	0.641 (0.34, 1.20)	0.1663	0.508 (0.27, 0.96)	0.0385	0.507 (0.27, 0.96)	0.0364	0.474 (0.26, 0.88)	0.0186
Delta	1.889 (0.57, 6.31)	0.3012	1.929 (0.64, 5.79)	0.2412	1.903 (0.70, 5.21)	0.2103	2.181 (1.06, 4.49)	0.0346	2.189 (1.05, 4.57)	0.0369	2.967 (1.43, 6.15)	0.0035	0.823 (0.40, 1.69)	0.5952	0.884 (0.44, 1.79)	0.7321	0.910 (0.46, 1.78)	0.7842
Epsilon	1.670 (0.32, 8.81)	0.5458	1.665 (0.32, 8.76)	0.5471	1.652 (0.32, 8.54)	0.5492	1.350 (0.25, 7.35)	0.7283	1.545 (0.31, 7.81)	0.5984	1.573 (0.31, 8.03)	0.5859	0.882 (0.14, 5.40)	0.8918	0.933 (0.16, 5.52)	0.9395	1.134 (0.22, 5.87)	0.8808
Gamma	1.282 (0.42, 3.93)	0.6634	1.302 (0.43, 3.91)	0.6383	1.269 (0.43, 3.76)	0.6674	1.196 (0.41, 3.47)	0.7422	1.117 (0.38, 3.28)	0.8404	1.384 (0.48, 3.98)	0.5471	0.914 (0.31, 2.73)	0.8719	0.920 (0.31, 2.73)	0.8805	0.854 (0.29, 2.51)	0.7748
Iota	0.893 (0.46, 1.75)	0.743	0.912 (0.47, 1.78)	0.787	0.889 (0.46, 1.73)	0.7282	0.792 (0.41, 1.52)	0.4838	0.814 (0.43, 1.55)	0.5321	0.861 (0.45, 1.66)	0.6547	0.612 (0.31, 1.20)	0.1545	0.646 (0.33, 1.26)	0.2009	0.594 (0.31, 1.15)	0.12
Mu	2.283 (0.65, 8.00)	0.1969	2.704 (0.84, 8.76)	0.097	2.684 (0.89, 8.12)	0.0803	2.408 (0.97, 6.01)	0.0595	2.884 (1.15, 7.25)	0.0244	3.718 (1.49, 9.28)	0.0049	0.962 (0.38, 2.45)	0.9346	1.251 (0.50, 3.16)	0.6357	1.246 (0.51, 3.04)	0.63
Omicron BA.1	2.982 (0.76, 11.74)	0.1182	2.841 (0.84, 9.66)	0.0945	2.661 (0.90, 7.91)	0.0782	3.010 (1.29, 7.03)	0.0109	2.914 (1.24, 6.86)	0.0144	3.791 (1.63, 8.82)	0.002	1.236 (0.53, 2.89)	0.625	1.314 (0.58, 2.99)	0.5154	1.240 (0.57, 2.72)	0.5906
Omicron BA.2	3.726 (0.89, 15.65)	0.0725	3.487 (0.97, 12.53)	0.0556	3.264 (1.05, 10.13)	0.0407	3.189 (1.26, 8.05)	0.0141	3.026 (1.21, 7.59)	0.0183	4.060 (1.63, 10.10)	0.0026	1.412 (0.56, 3.59)	0.4688	1.465 (0.59, 3.62)	0.4078	1.428 (0.60, 3.37)	0.4164
Omicron BA.4	1.803 (0.35, 9.23)	0.4792	1.912 (0.43, 8.45)	0.3928	1.808 (0.47, 6.94)	0.388	1.434 (0.43, 4.80)	0.5587	1.592 (0.48, 5.23)	0.4438	2.181 (0.68, 7.00)	0.1897	0.699 (0.21, 2.35)	0.563	0.833 (0.26, 2.72)	0.7613	0.816 (0.26, 2.52)	0.7241
Omicron BA.5	3.846 (0.83, 17.91)	0.0862	3.530 (0.89, 13.97)	0.0724	3.303 (0.97, 11.30)	0.0569	3.089 (1.07, 8.95)	0.0378	2.889 (1.02, 8.21)	0.0466	3.818 (1.36, 10.71)	0.0109	1.441 (0.49, 4.23)	0.5067	1.446 (0.51, 4.08)	0.4861	1.369 (0.51, 3.68)	0.5342

Supplemental Table 2: Interval 1 Variants by Vaccination Status

	Alpha & Other-VOCs (n=44)	Delta (n=48)
Vaccination Status		
0 doses	39 (88.6%)	39 (81.3%)
1 dose ≥5 months	0 (0.0%)	1 (2.1%)
1 dose <5 months	0 (0.0%)	2 (4.2%)
2 doses ≥5 months	1 (2.3%)	1 (2.1%)
2 doses <5 months	4 (9.1%)	5 (10.4%)

Supplemental Table 3: Interval 1 Logistic Regression Model

Covariates	Odds ratio (e^{β}, 95% CI)	p-value
Vaccination status		
Unvaccinated	Ref.	Ref.
1 dose ≥5 months	1.670×10^{8}	0.998
1 dose <5 months	1.158×10^{8}	0.997
2 doses ≥5 months	0.295 (0.02, 5.36)	0.409
2 doses <5 months	2.577 (0.38, 17.27)	0.329
Age category		
≤ 4	Ref.	Ref.
5-17	1.581 (0.12, 20.49)	0.726
18-39	2.773 (0.26, 29.93)	0.401
40-64	3.092 (0.25, 37.71)	0.376
≥ 65	0.223 (0.01, 4.93)	0.342
Sex		
Male	Ref.	Ref.
Female	1.715 (0.57, 5.17)	0.339
Time	4.096 (2.13, 7.88)	<0.0001

Supplemental Table 4: Interval 2 Variants by Vaccination Status

	Delta (n=446)	Omicron BA.1 (n=414)
Vaccination Status		
0 doses	162 (36.3%)	160 (38.6%)
1 dose ≥5 months	41 (9.2%)	26 (6.3%)
1 dose <5 months	7 (1.6%)	8 (1.9%)
2 doses ≥5 months	202 (45.3%)	176 (42.5%)
2 doses <5 months	24 (5.4%)	20 (4.8%)
3 doses <5 months	10 (2.2%)	24 (5.8%)

Supplemental Table 5: Interval 2 Logistic Regression Model

Covariates	Odds ratio (e^{β}, 95% CI)	p-value
Vaccination status		
Unvaccinated	Ref.	Ref.
1 dose ≥5 months	0.664 (0.24, 1.84)	0.431
1 dose <5 months	0.710 (0.12, 4.35)	0.7112
2 doses ≥5 months	2.093 (1.11, 3.94)	0.022
2 doses <5 months	0.420 (0.12, 1.46)	0.171
3 doses <5 months	7.118 (1.44, 35.17)	0.016
Age category		
≤ 4	Ref.	Ref.
5-17	1.785 (0.21, 15.53)	0.600
18-39	6.298 (0.73, 54.23)	0.094
40-64	2.586 (0.30, 22.59)	0.390
≥ 65	1.819 (0.19, 17.83)	0.608
Sex		
Male	Ref.	Ref.
Female	0.956 (0.57, 1.60)	0.866
Time	57.150 (31.00, 105.36)	<0.0001

Supplemental Table 6: Interval 3 Variants by Vaccination Status

	Omicron BA.1 (n=314)	Omicron BA.2 (n=391)
Vaccination Status		
0 doses	120 (38.2%)	118 (30.2%)
1 dose ≥5 months	14 (4.5%)	23 (5.9%)
1 dose <5 months	4 (1.3%)	9 (2.3%)
2 doses ≥5 months	83 (26.4%)	121 (30.9%)
2 doses <5 months	18 (5.7%)	16 (4.1%)
3 doses ≥5 months	13 (4.1%)	19 (4.9%)
3 doses <5 months	62 (19.7%)	85 (21.7%)

Supplemental Table 7: Interval 3 Logistic Regression Model

Covariates	Odds ratio (e^{β}, 95% CI)	p-value
Vaccination status		
Unvaccinated	Ref.	Ref.
1 dose ≥5 months	1.326 (0.57, 3.08)	0.512
1 dose <5 months	2.639 (0.62, 11.29)	0.191
2 doses ≥5 months	1.343 (0.84, 2.15)	0.219
2 doses <5 months	0.881 (0.36, 2.18)	0.784
3 doses ≥5 months	1.113 (0.42, 2.98)	0.832
3 doses <5 months	1.158 (0.69, 1.96)	0.582
Age category		
≤ 4	Ref.	Ref.
5-17	4.587 (1.35, 15.59)	0.015
18-39	4.038 (1.25, 13.04)	0.020
40-64	4.068 (1.26, 13.12)	0.019
≥ 65	5.266 (1.49, 18.60)	0.010
Sex		
Male	Ref.	Ref.
Female	1.045 (0.73, 1.49)	0.811
Time	3.099 (2.53, 3.80)	<0.0001

Supplemental Table 8: Interval 4 Variants by Vaccination Status

	Omicron BA.2 (n=319)	Omicron BA.4/5 (n=355)
Vaccination Status		
0 doses	109 (34.2%)	111 (31.3%)
1 dose ≥5 months	22 (6.9%)	17 (4.8%)
1 dose <5 months	2 (0.6%)	0 (0.0%)
2 doses ≥5 months	98 (30.7%)	97 (27.3%)
2 doses <5 months	1 (0.3%)	2 (0.6%)
3 doses ≥5 months	77 (24.1%)	105 (29.6%)
3 doses <5 months	5 (1.6%)	11 (3.1%)
4 doses	5 (1.6%)	12 (3.4%)

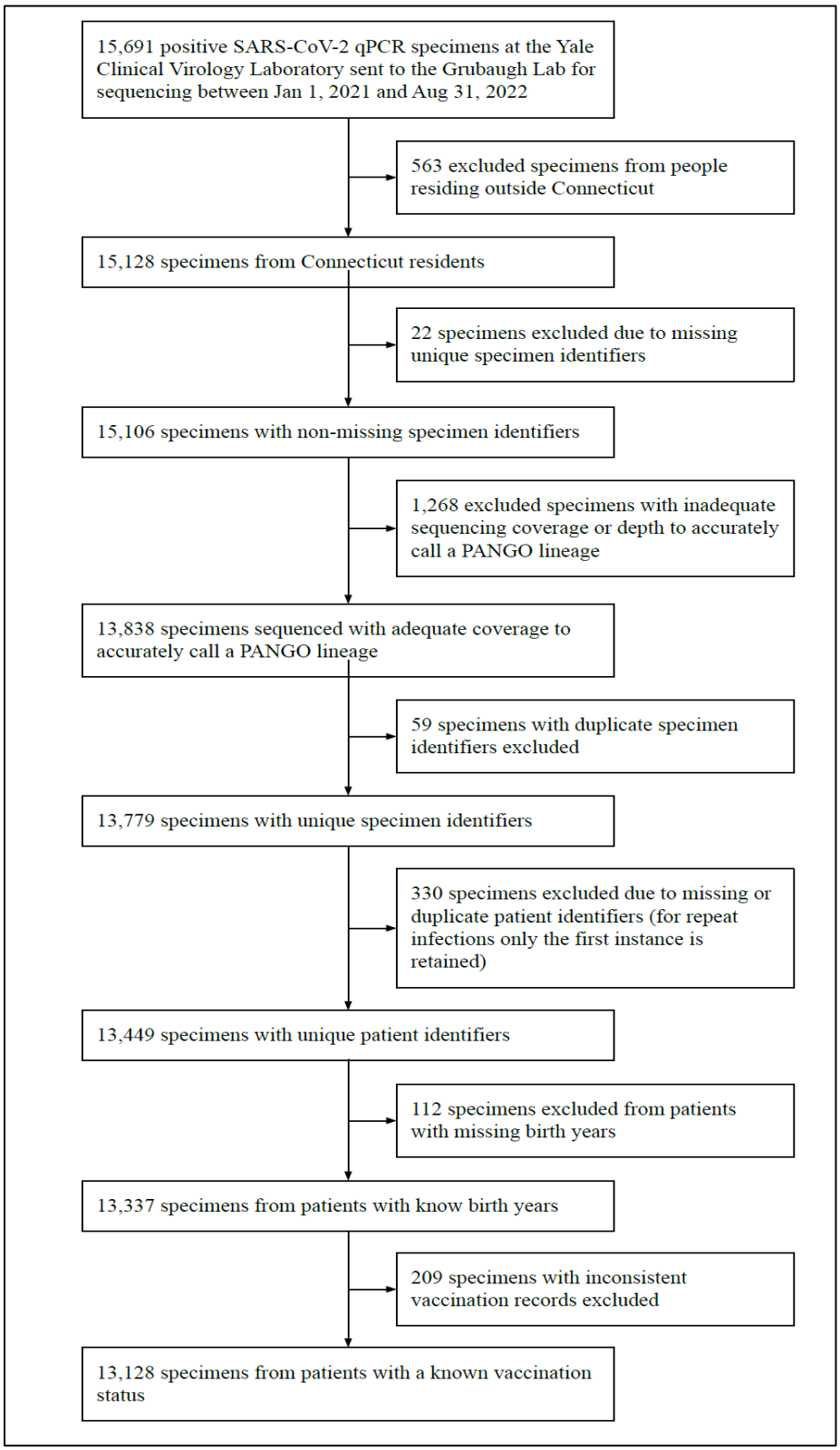
Supplemental Table 9: Interval 4 Logistic Regression Model

Covariates	Odds ratio (e^{β}, 95% CI)	p-value
Vaccination status		
Unvaccinated	Ref.	Ref.
1 dose ≥5 months	0.912 (0.41, 2.03)	0.821
1 dose <5 months	0	0.992
2 doses ≥5 months	0.981 (0.61, 1.58)	0.936
2 doses <5 months	2.261 (0.11, 45.71)	0.595
3 doses ≥5 months	1.567 (0.95, 2.58)	0.079
3 doses <5 months	2.913 (0.84, 10.10)	0.092
4 doses <5 months	2.080 (0.58, 7.46)	0.261
Age category		
≤ 4	Ref.	Ref.
5-17	1.170 (0.47, 2.91)	0.736
18-39	1.372 (0.63, 2.98)	0.424
40-64	1.167 (0.53, 2.57)	0.702
≥ 65	0.833 (0.36, 1.95)	0.674
Time	2.889 (2.36, 3.54)	<0.0001

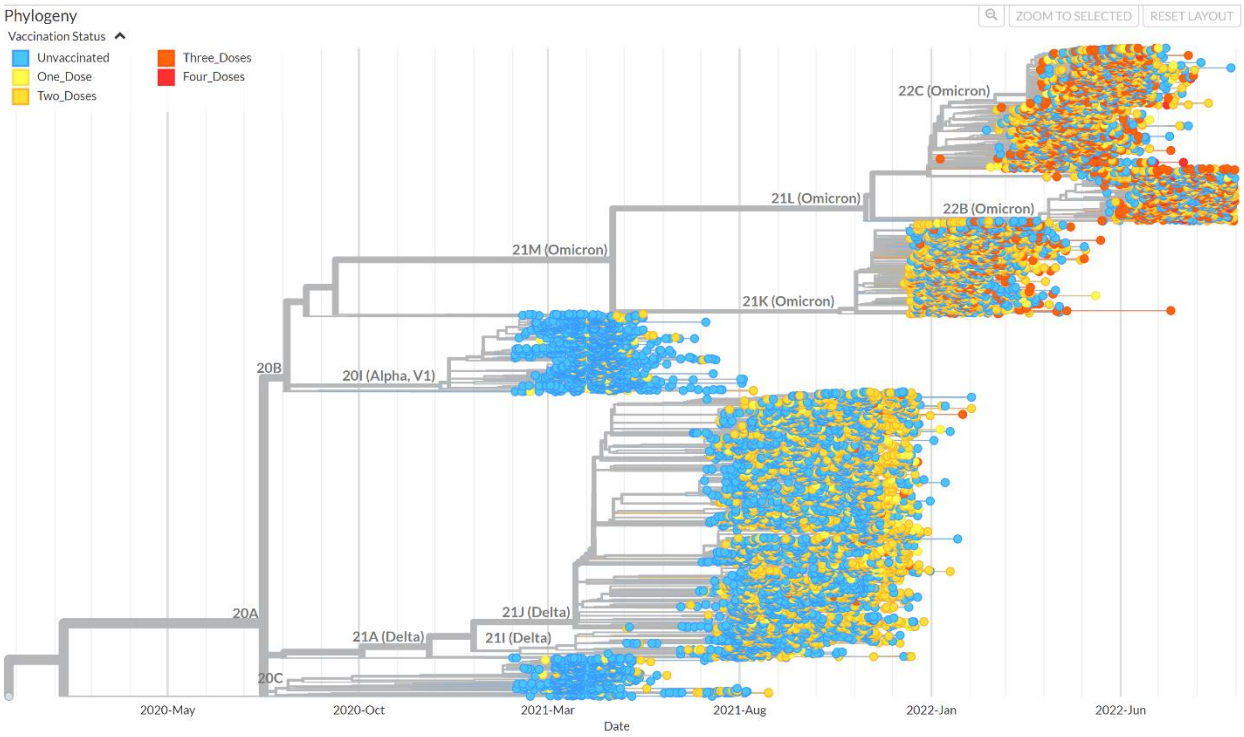
Supplemental Table 10: Interval 4 Logistic Regression Model (Aggregated)

Covariates	Odds ratio (e^{β}, 95% CI)	p-value
Vaccination status		
Unvaccinated	Ref.	Ref.
1 dose	0.848 (0.38, 1.87)	0.683
2 doses	0.999 (0.62, 1.61)	0.998
3 doses	1.663 (1.01, 2.73)	0.044
4 doses	2.124 (0.59, 7.63)	0.248
Age category		
≤ 4	Ref.	Ref.
5-17	1.185 (0.47, 2.96)	0.716
18-39	1.379 (0.63, 3.01)	0.420
40-64	1.136 (0.51, 2.51)	0.753
≥ 65	0.819 (0.35, 1.93)	0.647
Time	2.892 (2.35, 3.55)	<0.0001

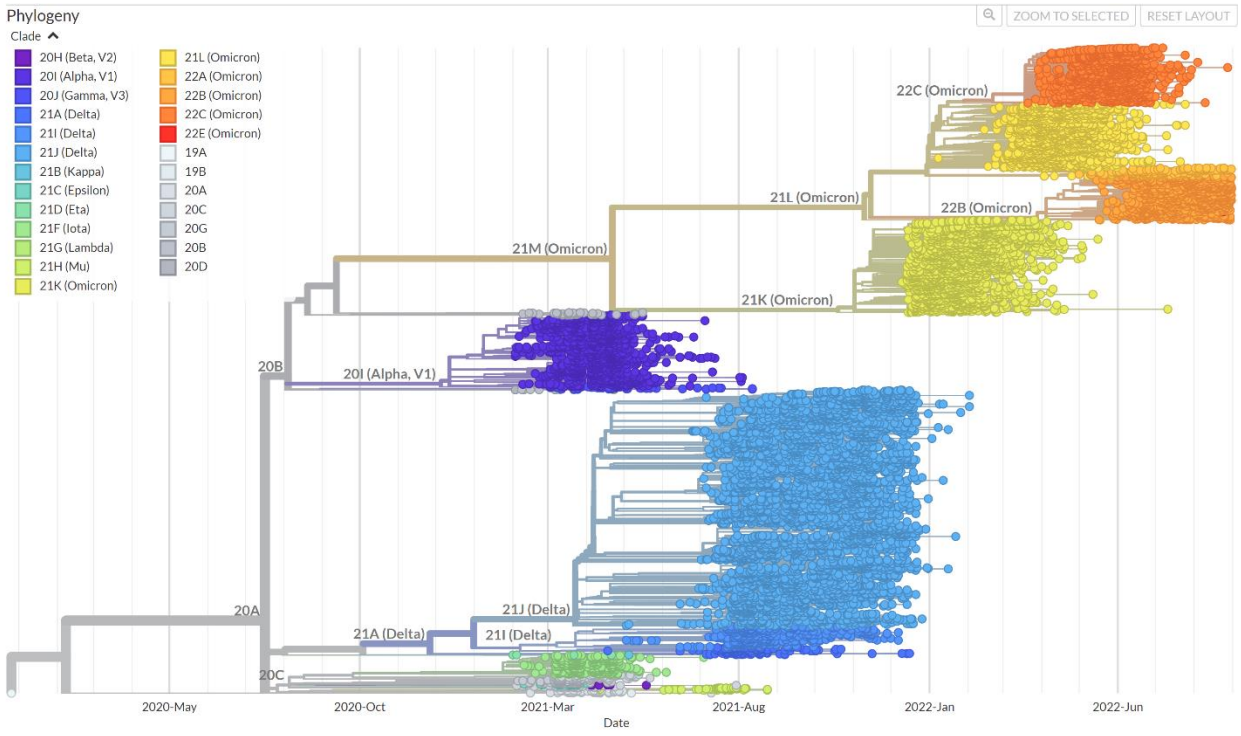
Supplemental Figure 1



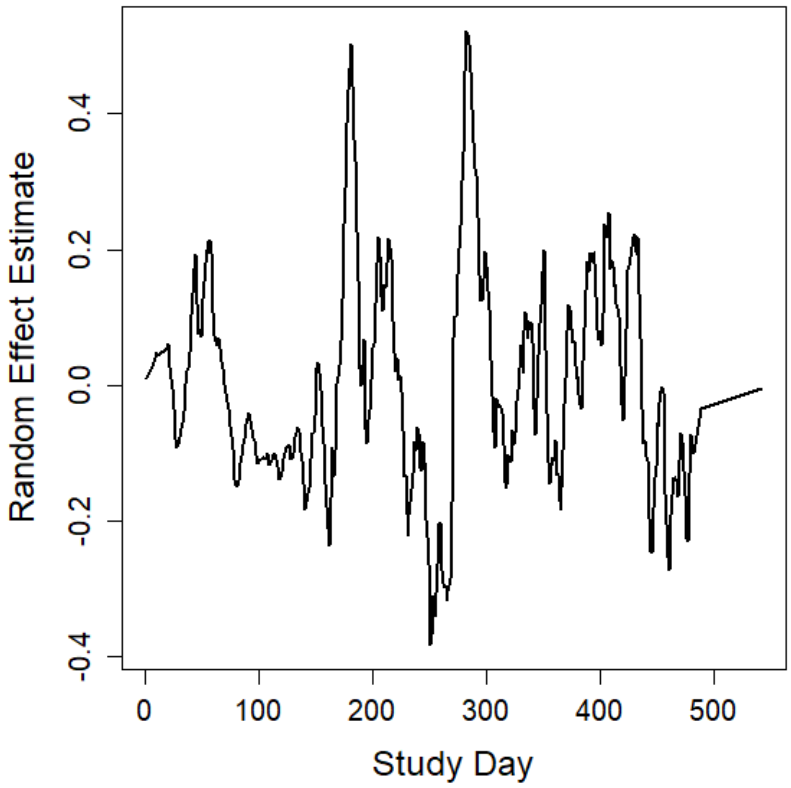
Supplemental Figure 2: Phylogenetic tree of study sequences by breakthrough status



Supplemental Figure 3: Phylogenetic tree of study sequences by variant lineage



Supplemental Figure 4: Random effect estimates over time



Supplemental Document 1: Available upon request