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Pre-Existing Population Immunity and severe acute respiratory syndrome coronavirus 2 Variant Establishment and Dominance Dynamics in the United States: An Ecological Study

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We conducted an ecological analysis of the dynamics of Delta and Omicron establishment and dominance in US states. Omicron became the dominant circulating variant later in states with higher population-level immunity. By contrast, population immunity did not impact the maximum rate of takeover by Delta or Omicron from prior variants.

Keywords. Delta Omicron immunity COVID-19.

The pandemic of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has been characterized by the emergence of variants with competitive advantages in transmissibility and/or the capacity to evade pre-existing immunity [1]. A quantitative framework to understand how new variants displace circulating strains and the impact of population immunity on these dynamics is critical to inform public health preparedness for future waves.

Two recent variants of concern, Delta and Omicron, became the dominant variants in all areas of the world, including those with high rates of previous vaccination or infection [2]. However, these variants became dominant under relatively different circumstances of competition with previously circulating strains. Whereas the Delta variant was slightly more immune evasive than its predecessor, the Alpha variant, the Omicron variant is considerably more immune evasive than Delta [1]. In the United States, SARS-CoV-2 population immunity has historically varied considerably by state due to different rates of prior infection and vaccine uptake [3]. Yet, it remains unclear how this variability impacts the timing of establishment and dominance of variants with different immune evasiveness characteristics.

We performed an ecological study using publicly available data to assess the relationship between population immunity to SARS-CoV-2 and the rate, date, and timing of variant takeover at a state level in the United States. Although population immunity is challenging to assess, we estimated it using a metric comprising a combination of vaccine uptake, which is well defined, and prior infections, which are incompletely captured. We used publicly reported seroprevalence measures of antibodies to both nucleocapsid (virus exposure) and spike (virus or vaccination) to cross-check these metrics, and given the inherent uncertainty in these estimates, we performed sensitivity analyses to assess the impact of different plausible ranges on the conclusions reached. We hypothesized that if immune evasion was a major driver of variant dominance dynamics, then both variants would become dominant sooner and faster in states with higher levels of pre-existing immunity, with a greater effect during Omicron takeover.

METHODS

Severe Acute Respiratory Syndrome Coronavirus 2 Variant Data Sources and Definitions

We accessed SARS-CoV-2 genomic sequence data submitted to the Global Initiative on Sharing Avian Influenza Data (GISAID) from all 50 US states between January 1 and August 31, 2021 and between November 24, 2021 and February 8, 2022 [4]. These periods spanned from the first detections of Delta and Omicron, respectively, to a time when each consistently represented >99% of all sequenced genomes. For each period, we extracted the proportion of the emerging variant among total SARS-CoV-2 sequences, computed as 7-day averages. We identified the initial week during which a variant was first sequenced and designated it as the week of variant emergence if at least 1 additional isolate of the variant was identified within the subsequent 3 weeks. This constraint was implemented to avoid misclassifying stochastic introductions of a variant without subsequent sustained transmission as the true emergence of a new variant, a phenomenon that can be observed on occasion with overdispersed spread [5]. It affected 7 states during Delta emergence, and no states during Omicron emergence.

Modeling/Statistical Methods to Evaluate Variant Takeover

We fit asymmetric logistic growth curves to changes in variant proportion over time and obtained curve-fit estimates for (1)

maximum slope; (2) inflection point, that is, the time at which variant proportion was 50%; and (3) time at which variant proportion was 10% [6]. In line with epidemiological reality, the lower and upper asymptotes of the curves were fixed at 0% and 100%, respectively. Using these data, we derived 3 outcome measures of variant takeover: (1) takeover rate, defined as the maximum slope of the logistic curve; (2) calendar date of variant dominance, estimated as the date variant proportion exceeded 50%; and (3) time from establishment to dominance, computed as the time taken for variant proportion to increase from 10% to 50%. We estimated the calendar date of dominance to mitigate against the effect of variation in fractions of sequenced cases in different states impacting the likelihood of variant discovery, which would in turn alter the observed time to dominance. Ten percent variant fraction was chosen to define variant establishment to minimize the effect of stochastic fluctuations at lower variant fractions [7].

Population Immunity Data Sources and Definitions

Using US Centers for Disease Control (CDC) data of cumulative SARS-CoV-2 cases and vaccinations in each state [8], we estimated immunity to coronavirus disease 2019 using 3 definitions: (1) proportion immune from vaccination; (2) proportion immune from infection with an earlier variant; and (3) proportion immune from either prior vaccination or infection. We estimated the proportion with prior infection by comparing anti-nucleocapsid (anti-N) antibody seroprevalence (elicited by infection) [9] with reported cases to compute case underreporting multipliers for each state, then we used the multipliers to estimate daily case incidence [3]. We computed the fraction of the population that had either received a primary vaccine series only or been boosted. Assuming a 2-week delay between exposure and attainment of immunity [10], we used efficacy estimates for vaccine-induced and infection-induced immunity to separately estimate the proportion of individuals immune from infection or vaccination. We incorporated the effect of waning immunity by adjusting the efficacy of immunity based on time since exposure [11–13], using parameters summarized in Supplementary Table S1. We approximated combined immunity from infection or vaccination by estimating the fraction of the population without immunity as $w = (1-p) \times (1-v)$, where p and v are the previously infected and vaccinated proportions, respectively, then computing the total proportion immune as $1-w$ [14]. We also collated anti-spike (anti-S) antibody seroprevalence (elicited by either infection or vaccination) during variant takeover [15]. These data are reported by geographic region, and we retrieved estimates for 46 states that corresponded to the geographic regions.

For each measure of variant takeover, we fit linear regression models to estimate the relationship with estimates of population immunity across different states. Code for the analysis

and collated datasets (Supplementary Table S2) are available at github.com/pankomah/variant_immunity.
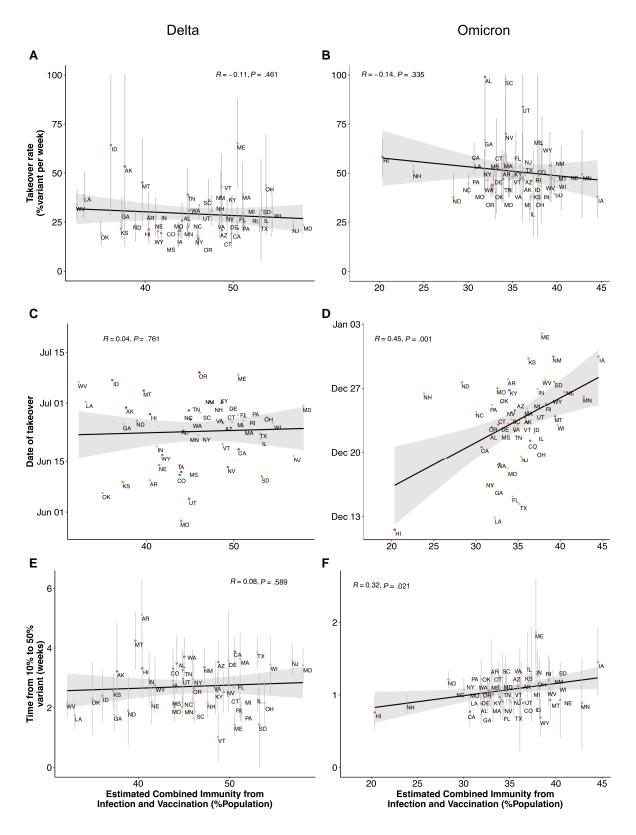
RESULTS

We fit logistic curves to estimate the proportion of SARS-CoV-2 infections attributable to Delta or Omicron variants in each state during the transition (1) from Alpha and other circulating variants to Delta and (2) from Delta to Omicron (Supplementary Figure S1). The GISAID estimates of variant proportions used to fit these logistic curves closely matched variant proportion data from the US CDC [8] (Supplementary Table S3). By incorporating vaccinations (including primary series and boosters) and estimates of prior infections, adjusted by estimates of waning based on time since vaccination or infection, we computed estimated effective population immunity for each variant in each state over time.

In Figure 1, we graphically depict the relationship between variant takeover and this estimated effective population immunity. There was no statistically significant relationship between variant takeover rates and immunity for Delta ($R = -0.11$, $P = .461$) (Figure 1A) or Omicron ($R = -0.14$, $P = .335$) (Figure 1B). Takeover for Omicron occurred at later dates in states with more immune populations ($R = 0.45$, $P = .001$) (Figure 1D), but not for Delta ($R = 0.04$, $P = .761$) (Figure 1C). There was also a statistically significant difference in time from establishment (10%) to dominance (50%) for Omicron ($R = 0.32$, $P = .021$) (Figure 1F), occurring over a longer period in states with higher population immunity, but not for Delta ($R = 0.08$, $P = .589$) (Figure 1E).

Given substantial uncertainty in estimating effective population immunity, we conducted 3 sensitivity analyses: (1) substituting seroprevalence for our combined immunity metric; (2) assessing vaccination alone, as the measure of immunity that can be most precisely captured and for which efficacy against each variant over time has been most systematically studied; and (3) analyzing the time from initial detection of each variant to its establishment (10%) in each state. We found that adult seroprevalence estimates did not demonstrate any significant relationship with takeover metrics (Supplementary Figure S2). When we compared variant takeover to estimated immunity from vaccination alone, there was no relationship between immunity and takeover rates, a statistically significant delay in Delta takeover date ($P = .01$) and time from establishment to dominance ($P = .011$) for Omicron in states with higher vaccine-induced immunity, and a nonsignificant trend to delayed takeover date for Omicron in more vaccinated states

Figure 1. Delta and Omicron variant takeover and immunity in different US states. Maximum takeover rates of (*A*) Delta and (*B*) Omicron in different states. Estimated calendar dates at which (*C*) Delta and (*D*) Omicron reached 50% of sequenced severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) genomes in different states (date of takeover). Estimated time taken for proportion of (*E*) Delta and (*F*) Omicron to increase from 10% to 50% of sequenced SARS-CoV-2 genomes in different states. States are identified by standard 2-letter abbreviations; states in the same census geographic region are plotted with the same color. Error bars for takeover rates were limited to maxima and minima of 100 and 0, respectively. Immunity is estimated by the combined proportion of the state's population immune from SARS-CoV-2 infection with an earlier variant or vaccination before variant proportion exceeding 50%. Linear regressions are shown in black with 95% confidence intervals in gray shading. Pearson correlation coefficient (R) and *P* value test results are shown for each plot.

($P = .074$) (Supplementary Figure S3). We also evaluated the relationship between immunity and the time from first detection to establishment for both variants. In states with higher immunity, it took longer for Delta to establish, whereas for Omicron, there was a nonstatistically significant trend towards later date of establishment (Supplementary Figure S4).

DISCUSSION

In this ecological study, we tested the hypothesis that novel immune-evasive SARS-CoV-2 variants would become dominant faster in states with higher levels of population immunity. Contrary to our hypothesis, we found no statistically significant association between takeover rates of Delta or Omicron and state-level immunity. Instead, we observed later takeover for Omicron in more immune states.

These results suggest that either population-level immunity did not affect the rates at which the Delta or Omicron variants took over, or that other properties affecting transmission by state either counterbalanced or outweighed any such effects. Although immune-evasive variants are expected to transmit better among immune individuals than less-evasive variants [16], we speculate that this might have been offset by decreased rates of secondary transmission in these same immune subpopulations. For example, longitudinal cohort studies have demonstrated that full vaccination and boosting decrease the secondary attack rate among contacts of individuals infected with Delta or Omicron, respectively, and accelerate the rate of viral clearance, thereby decreasing potential subsequent transmission events [17–19]. The observation of a statistically significant delay in date of and time to Omicron, but not Delta takeover, may then stem from the relatively greater ability of Omicron to infect immune subpopulations during its competitive circulation with Delta, more so than for Delta with Alpha. Although a trend towards later date of establishment could have contributed to the delayed takeover of Omicron, substantial uncertainty in variant detection at low fractions makes evaluation of variant establishment periods challenging. In addition, other explanations, either based on differences between states (eg, behavioral differences) or inherent to the viral variants (eg, relative transmissibility), may also contribute to the observed trends.

Important caveats to our observations include limitations associated with use of publicly available data, including case underreporting and sequence data whose depth and representativeness may vary by state. Population immunity estimates from infection and vaccination are challenging due to multiple factors, including case underreporting, inherent uncertainty around the overlap between vaccinated and infected subpopulations, and consequent difficulty with accurately computing frequency of and protection from hybrid immunity. However, alternative seroprevalence data reflect exposure but not necessarily effective immunity. In addition, unmeasured confounders such as public health mitigation policies, behaviors, or population density may systematically vary by state and concurrently affect both vaccination rates and variant transmission.

CONCLUSIONS

Nevertheless, our results suggest that population-level data on vaccination and infection rates alongside assessments of changing variant proportion may provide a useful framework to understand how population immunity affects circulating SARS-CoV-2 variants. This may be particularly important as Omicron sublineages successively displace prior ones, leading regulatory and public health agencies to consider strategies for deploying updated vaccines. Our findings do not support theoretical concerns about enhanced selection for immune-evasive variants as a drawback of widespread vaccination campaigns, since states with more measured immunity saw similar maximum takeover rates and similar or later time to dominance of emerging variants. Updated vaccines may thus improve protection against currently circulating lineages without hastening the takeover of future variants. Given their remarkable efficacy against severe or fatal disease [20], and lack of discernible difference in takeover rates of immune-evasive variants, vaccines remain a cornerstone of pandemic mitigation.

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