

Early Introduction and Rise of the Omicron Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Variant in Highly Vaccinated University Populations

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Background. The Omicron variant of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is highly transmissible in vaccinated and unvaccinated populations. The dynamics that govern its establishment and propensity toward fixation (reaching 100% frequency in the SARS-CoV-2 population) in communities remain unknown. Here, we describe the dynamics of Omicron at 3 institutions of higher education (IHEs) in the greater Boston area.

Methods. We use diagnostic and variant-specifying molecular assays and epidemiological analytical approaches to describe the rapid dominance of Omicron following its introduction into 3 IHEs with asymptomatic surveillance programs.

Results. We show that the establishment of Omicron at IHEs precedes that of the state and region and that the time to fixation is shorter at IHEs (9.5–12.5 days) than in the state (14.8 days) or region. We show that the trajectory of Omicron fixation among university employees resembles that of students, with a 2- to 3-day delay. Finally, we compare cycle threshold values in Omicron vs Delta variant cases on college campuses and identify lower viral loads among college affiliates who harbor Omicron infections.

Conclusions. We document the rapid takeover of the Omicron variant at IHEs, reaching near-fixation within the span of 9.5–12.5 days despite lower viral loads, on average, than the previously dominant Delta variant. These findings highlight the transmissibility of Omicron, its propensity to rapidly dominate small populations, and the ability of robust asymptomatic surveillance programs to offer early insights into the dynamics of pathogen arrival and spread.

Keywords. SARS-CoV-2; epidemiology; infectious disease surveillance.

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In the final days of 2021, the global severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) case count surpassed 1 million cases per day [1], with the surge due, at least in part, to the Omicron variant of concern (B.1.1.529). In the United States, coronavirus disease 2019 (COVID-19) case counts reached record highs (3–5 times the peak of prior waves), with the estimated percentage of cases due to Omicron rapidly increasing from <1% of cases (4 December 2021) to >95% of cases (1 January 2022) [2]. Omicron transmission is possible

among both vaccinated and unvaccinated individuals [3], although the relative rates of transmission from each remain unclear. Evidence suggests that Omicron can partially evade immunity acquired from prior COVID-19 infection [4] and from a 2-dose messenger RNA (mRNA) vaccine regimen [5], though a third dose improves Omicron neutralization efficiency, at least in the short term [6].

To mitigate the risks of congregate living, institutes of higher education (IHEs) use a combination of vaccination requirements [7, 8], high-frequency testing [8, 9], and behavioral interventions such as masking and social distancing to control viral spread. An analysis [10] suggests that in the setting of masking and frequent testing, case counts are not correlated with dorm occupancy or in-person instruction; this is consistent with the evidence that cases have been predominantly acquired in off-campus settings [11]. Moreover, detailed genomic analyses of an IHE and its nearby communities suggested that transmission dynamics within the IHE did not result in spread to the greater community [12]. Thus, many IHEs successfully controlled the spread of COVID-19 through the Delta surge. However, in December 2021, COVID-19 case counts rose rapidly both in college communities [13] and in New England (NE) as a whole, with viral genomic sequencing confirming Omicron as the cause. While some institutions responded by converting to distance learning or requiring booster shots [14–18], the feasibility of maintaining residential college life without another spike in cases was in question.

Here, we capitalize on asymptomatic testing programs at 3 Boston-based IHEs, Boston University (BU), Harvard University (HU), and Northeastern University (NU), to document the rapid takeover of the Omicron variant, reaching near-fixation within the span of 9.5–12.5 days despite lower viral loads, on average, than the previously dominant Delta (B.1.627.2) variant.

METHODS

Patient Samples and Ethics Statement

We gathered de-identified sample information from 3 institutions with campus testing programs [11] (Table 1). We received the following information for every positive test collected between 2 December 2021 and 21 December 2021: sample collection date, cycle threshold (Ct) for 1 or more genes, and variant designation. From BU, we also received affiliate status (student vs employee, where employees include faculty, staff, and contractual employees). For HU, SARS-CoV-2 samples were collected from consented individuals under the Harvard Longwood Campus institutional review board (IRB) 20-1877 and covered by an exempt determination (EX-7295) at the Broad Institute. For BU, SARS-CoV-2 samples and data access were covered by an exemption determination under BU IRB

6122E. The use of these data in this study was evaluated and approved by NU under data use agreement 20-1481.

Experimental Methods

Across universities, individuals self-collected anterior nares specimens, which were analyzed using reverse transcription quantitative polymerase chain reaction (RT-qPCR). At BU, a 2-target SARS-CoV-2 assay with RNase P control was performed [11, 22]. At HU, the Quaris SARS-CoV-2 assay was performed [23]. At NU, the Thermo Fisher Scientific Applied Biosystems TaqPath COVID-19 Combo Kit was used [24]. Variant status was assessed using amplicon-based viral sequencing, as previously described [25] (BU); mCARMEN [26], a CRISPR-based diagnostic platform that identifies unique combinations of Spike gene mutations (HU); a variant-specific PCR assay (HU; Supplementary Table 1); or S-gene target failure [27] (SGTF; NU; Supplementary Methods).

Data Curation

We downloaded Massachusetts (MA) and NE case count data from the Centers for Disease Control and Prevention [28] and sequence data from the Global Initiative on Sharing All Influenza Data (GISAID) [29–31]. We removed 152 of 1758 samples (8.6%) from the universities (50 from BU and 102 from HU) with missing variant information (ie, due to assay technical limitations) from all subsequent analyses. We removed 53 of the 22 211 (0.2%) MA sequences from GISAID that had a variant classification other than Delta or Omicron. We removed 22 211 of the 30 796 (72.1%) NE sequences from GISAID [29–31] that were in MA (ie, NE curve fits do not include MA) and 29 of the remaining 8585 (0.3%) sequences that had a variant classification other than Delta or Omicron. We removed 20 gene-specific data points with Ct >40 or Ct <5 due to possible technical errors. For Ct comparisons, samples with missing data due to failed amplification of a specific gene were removed solely from the analysis of that gene. For the per-affiliation analyses, we removed 6 of 524 (1.1%) BU cases with missing student or employee designations.

Logistic Regression and Inference

We fit logistic models on binary variant calls as a function of the date, estimating the proportion of cases that were Omicron over time for each university individually (with data from 2 December–21 December), for MA and NE (with data from 1 December–1 January) and for BU by affiliation (student vs employee; with data from 2 December–21 December). We documented 95% confidence intervals (CIs) for our model's parameters, the overdispersion ratio, and McFadden's pseudo- R^2 (Supplementary Methods).

We estimated the date at which the Omicron fraction reached 10%, 50%, and 90%, hereafter defined as O_{10} , O_{50} , and O_{90} . We used the notation $\Delta O_{x, A-B} = O_{x, \text{Population A}} - O_{x, \text{Population B}}$ to

Table 1. Institutions Studied

Institute of Higher Education	Individuals in Testing Program ^a	Testing Frequency ^b (1/week)	Vaccination Rate ^b (1 Johnson & Johnson or 2 Messenger RNA)	Variant Designation Method	Cycle Threshold Gene ^c	Cases (2–21 December 2021)	Finals Week (2021)
Boston University	43 904	1	92.5% (employees, affiliates) 97.9% (students)	Viral sequencing	N1 N2 RNase P	524	14–18 December
Harvard University	38 434	3 (live on campus) 2 (live off campus, not vaccinated) 1 (live off campus, vaccinated)	97% (employees) 98% (students)	mCARMEN variant-specific polymerase chain reaction	N1	635	9–18 December
Northeastern University	30 602	1	97.7% (employees) 99.6% (students)	S-gene target failure	N1 ORF1ab S MS2	447	10–18 December

^aIndividuals in the testing programs include undergraduate and graduate students, faculty, and staff.

^bTesting frequencies and vaccination rates were collected from publicly available university dashboards [19–21].

^cN1, N2, ORF1ab, and S are severe acute respiratory syndrome coronavirus 2 genes; RNase P is a human gene (control); MS2 is a bacteriophage (control).

represent the difference in the date at which the Omicron fraction reached $x\%$ between 2 populations, and we used the notation $\Delta O_{90-10} = O_{90} - O_{10}$ to represent the number of days it took a particular population's Omicron fraction to rise from 10% to 90%.

We derived point estimates for O_x by inverting our regression model, such that:

$$O_x = \frac{\text{logit}\left(\frac{x}{100}\right) - B_0}{B_1},$$

where B_0 is the intercept and B_1 is the slope. To generate a standard error for O_x , we used the delta method [32, 33] with the transformation function $O_x(x)$ (as above) and with the mean and covariance of x determined by the coefficients and covariance matrix of our regression model, respectively.

We generated 95% CIs for O_x and compared O_x values between populations by approximating the distribution of O_x via the family of Student t distributions (Supplementary Methods).

Case Counts

For MA and NE, we summed confirmed and probable daily cases into the metric total daily cases. We noted weekly variation in case reporting (ie, no MA cases were reported on the weekends; Supplementary Figure 1) and thus calculated 7-day rolling averages. We noted smaller-scale variation in case count reporting at IHEs and calculated 3-day rolling averages. To approximate the number of MA cases that were Delta or Omicron, we used our logistic regression model to estimate the Omicron fraction for each day in 1 December–15 January. We scaled case counts by population sizes provided in Table 1 (IHEs) or in the 2020 census (MA) [34].

Ct Value Comparisons

We compared Ct values for Delta and Omicron cases per institution and per target, as each university had a unique testing protocol. We compared Ct values for the N1 (BU, HU), N2 (BU, NU), and ORF1ab (NU) genes. We also compared Ct values at BU per affiliation. We used the Wilcoxon rank sum test with Benjamini-Hochberg correction [35] to assess the relationship between SARS-CoV-2 variant and Ct.

RESULTS

There was a rapid increase in both daily case count and the Omicron fraction at IHEs in December 2021. In early December, Delta was circulating across MA and at IHEs, though case rates were higher per capita in the community outside of IHEs (Figure 1A). The Omicron surge at IHEs in mid-December was accompanied by a more modest rise in case counts (ie, slope of cases vs time) in MA and NE during the same period (note: testing rates were lower in these populations), followed by a striking regional surge in late December (Figure 1A, Supplementary Figure 1). A total of 1606 SARS-CoV-2 cases were identified across the 3 institutions (BU, HU, and NU) between 2 December (0% Omicron) and 21 December (91% Omicron). The fraction of cases that were Omicron across the IHEs, MA, and NE displayed a classic sigmoid-shaped curve consistent with logistic growth (Figure 1B, Supplementary Table 2), moving toward Omicron fixation. Delta diminished in frequency as well as total case count. By 5 January, the Harvard University Clinical Laboratory found that 100% of 159 samples tested were Omicron.

Omicron was established earlier and rose to fixation faster at IHEs than in MA as a whole (Figure 1B). We noted that MA

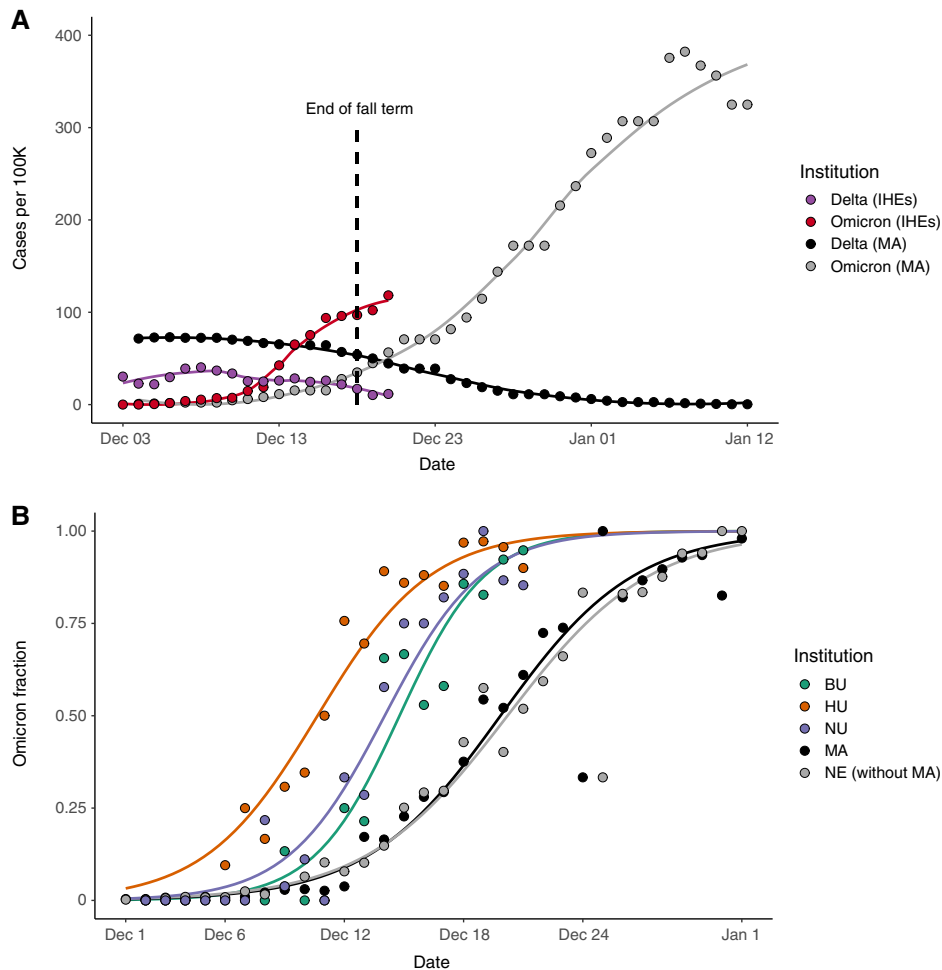


Figure 1. A, Cases per 100 000 across the IHEs and MA, stratified by variant. Plotted values are rolling averages over a 3-day (IHEs) or 7-day (MA) window to account for weekly variation in case reporting. Omicron and Delta variant proportions in MA were inferred from Global Initiative on Sharing All Influenza Data (GISAID) data (see the Methods section). The last day of fall semester finals occurred on 18 December (dashed line). Data from 3 December–20 December (IHEs) and 4 December–12 January (MA). B, Proportion of cases that were Omicron from 2 December–21 December (IHEs) and 1 December–1 January (MA, NE). Data were modeled using logistic regression. MA, Massachusetts data from GISAID. NE without MA, New England data (excluding the MA data) from GISAID. Abbreviations: BU, Boston University; HU, Harvard University; IHE, institutes of higher education; MA, Massachusetts; NE, New England; NU, Northeastern University.

and NE (without MA) had visually indistinguishable curves and fitted parameters with highly overlapping CIs (Supplementary Table 2). Thus, we compared the timing of Omicron's trajectory between IHEs and MA, with results generalizable to NE. To compare the timing of Omicron establishment across populations, we generated a metric (O_{10} ; see the Methods section) that estimates the date range at which 10% of the cases were Omicron. O_{10} occurred significantly earlier at IHEs than in MA, by an average of 2.4 days (BU), 3.8 days (NU), and 9.2 days (HU) (Table 2, Supplementary Table 3). To compare the duration at which Omicron fixated across populations, we generated the metric ΔO_{90-10} , the duration (in days) during which Omicron rose from 10% to 90% of cases (see the Methods section). ΔO_{90-10} was 9.5 at HU (95% CI, 9.2–9.8), 10.8 at BU (95% CI, 10.4–11.1), 12.5 at NU (95% CI, 12.1–12.9), and 14.8 in MA (95% CI, 14.8–14.9), indicating

that the trajectory to Omicron fixation occurred more rapidly at IHEs (Table 2). Taken together, these data point toward Omicron's earlier establishment and faster rise to fixation at IHEs compared with MA or NE.

Next, we found that BU employees displayed Omicron dynamics similar to those of BU students, with a 2–3 day delay in onset. We found no significant association between affiliation (student vs employee) and variant (Figure 2A; Fisher exact test, $P = .12$, odds ratio = 0.7 with 95% CI, .5–1.1), with employees accounting for 28.7% (74 Delta, 73 Omicron) of cases (1.13 per 100 employees) and students accounting for 71.3% (157 Delta, 214 Omicron; Figure 2B) of cases (1.20 per 100 students). We again used O_{10} (see the Methods section) to compare the timing of Omicron establishment between populations. O_{10} occurred significantly earlier among BU students relative to BU employees (by an average of 2.8 days)

Table 2. University-Specific Point Estimates and 95% Confidence Intervals for O_x and for ΔO_{90-10}

Institution	O_{10}	O_{10} 95% CI	O_{50}	O_{50} 95% CI	O_{90}	O_{90} 95% CI	ΔO_{90-10} (Days)	ΔO_{90-10} 95% CI (Days)
Harvard University	4 December	2–6 December	10 December	9–11 December	16 December	15–17 December	9.5	(9.2–9.8)
Northeastern University	8 December	7–10 December	14 December	13–14 December	19 December	18–20 December	12.5	(12.1–12.9)
Boston University	10 December	8–11 December	14 December	14–15 December	19 December	18–20 December	10.8	(10.4–11.1)
Massachusetts	12 December	12 December	19 December	19–20 December	27 December	27 December	14.8	(14.8–14.9)

O_x , the date at which the Omicron fraction equals x percent. ΔO_{90-10} , the duration of time that it takes the Omicron fraction to rise from 10% to 90%. CIs were generated via the Student t distribution, with estimation of the standard errors via the delta method (see the Methods section).

Abbreviation: CI, confidence interval.

and MA (by an average of 3.0 days; Figure 2C, Table 3, Supplementary Table 5). We compared ΔO_{90-10} as a metric of time to fixation, which was 8.5 among BU employees (95% CI, 7.9–9.1) and 9.5 among BU students (95% CI, 9.1–9.9; Table 3). ΔO_{90-10} was more comparable between BU students and employees than BU was to other IHEs (Table 2) and markedly differed in MA (14.8; 95% CI, 14.8–14.9), indicating that employees' trajectories resembled those of students (Table 3). Taken together, we found that employees and students had parallel Omicron trajectories with a lag time between 2 and 3 days.

Finally, we compared Ct values across variants and found that Omicron samples did not have lower Ct values (ie, higher viral loads) than Delta samples, suggesting that increased Omicron transmission is not driven by higher viral loads (Figure 3). At BU and HU, N1-gene Ct values were significantly higher, by an average of 2.2 ($P = .0002$) and 3.1 ($P < .0001$), respectively, in Omicron vs Delta samples (Figure 3A, 3B; Supplementary Table 6). This trend was recapitulated for N2-gene Ct values at BU (Omicron Ct values an average of 2.0 higher, $P = .0007$; Figure 3C, Supplementary Table 6). At NU, neither the N2- nor the ORFlab-gene Ct values differed by variant (Figure 3D, Supplementary Figure 2, Supplementary Table 6). We found no difference in BU's Ct values by affiliation status (ie, student vs employee; N1 gene, $P = .91$; N2 gene, $P = .81$), and we found that Ct-by-variant trends identified at BU are conserved when the data are conditioned on an affiliation (Supplementary Figure 3, Supplementary Table 7). In summary, we found that, despite differences in testing cadence, testing platform, and demographics among IHEs, Omicron viral Ct values were always higher than or indistinguishable from Delta Ct values.

DISCUSSION

Here, we document Omicron's swift spread through Boston-based IHEs in December 2021, which led to unprecedented increases in case counts. Though the IHEs and the urban environment in which they are located were experiencing Delta transmission at the time of Omicron introduction, Omicron rapidly became the dominant variant. Over an 9- to

13-day period, variant proportions converted from >90% Delta to >90% Omicron. Importantly, the rapid increase in Omicron case counts was identified in highly vaccinated populations in which Omicron's viral load, as inferred from anterior nares diagnostic Ct, was comparable to or lower than that of Delta. This is consistent with other reports that used throat or oropharyngeal swabs [36, 37], suggesting that the difference in viral loads is not specific to the anterior nares. This highlights that Omicron's fitness is neither driven by a higher viral load nor reliant on an immunologically naive population.

Though the date of establishment differed at the 3 IHEs, the dynamics of Omicron takeover were strikingly similar. The rapid rise in the Omicron fraction was offset by 1–4 days between universities, though we cannot rule out differences in testing cadence as the cause of the lag. The dynamics of Omicron dominance were similar across campuses despite differences in testing programs, on-campus vs off-campus housing, and variant designation technologies. Additionally, the time to fixation for BU employees was more comparable to that of BU students than that of the state, supporting a transmission mode that is independent of the residential nature of college campuses.

In contrast to the early establishment and dominance in the IHEs in our study, Omicron's procession toward fixation in MA occurred more slowly. While the difference in introduction time could be accounted for by earlier detection of cases in asymptomatic testing programs, the differences in slope and time to fixation cannot be explained by this factor. These dynamics are consistent with overdispersion in transmission, in which clusters of cases are responsible for the majority of spread, and the early stages of establishment within a community are stochastic and scale with the number of introductions [38, 39]. Overdispersion in SARS-CoV-2 transmission is well documented [38, 40–42], and our work is consistent with the continuation of this phenomenon with Omicron. IHEs are not siloed in their interaction networks; however, the proportion of interactions within an IHE's network is greater than the proportion of interactions that exit into the community; as a result, clusters of transmission are readily detected via robust screening. The ability of Omicron to rapidly spread

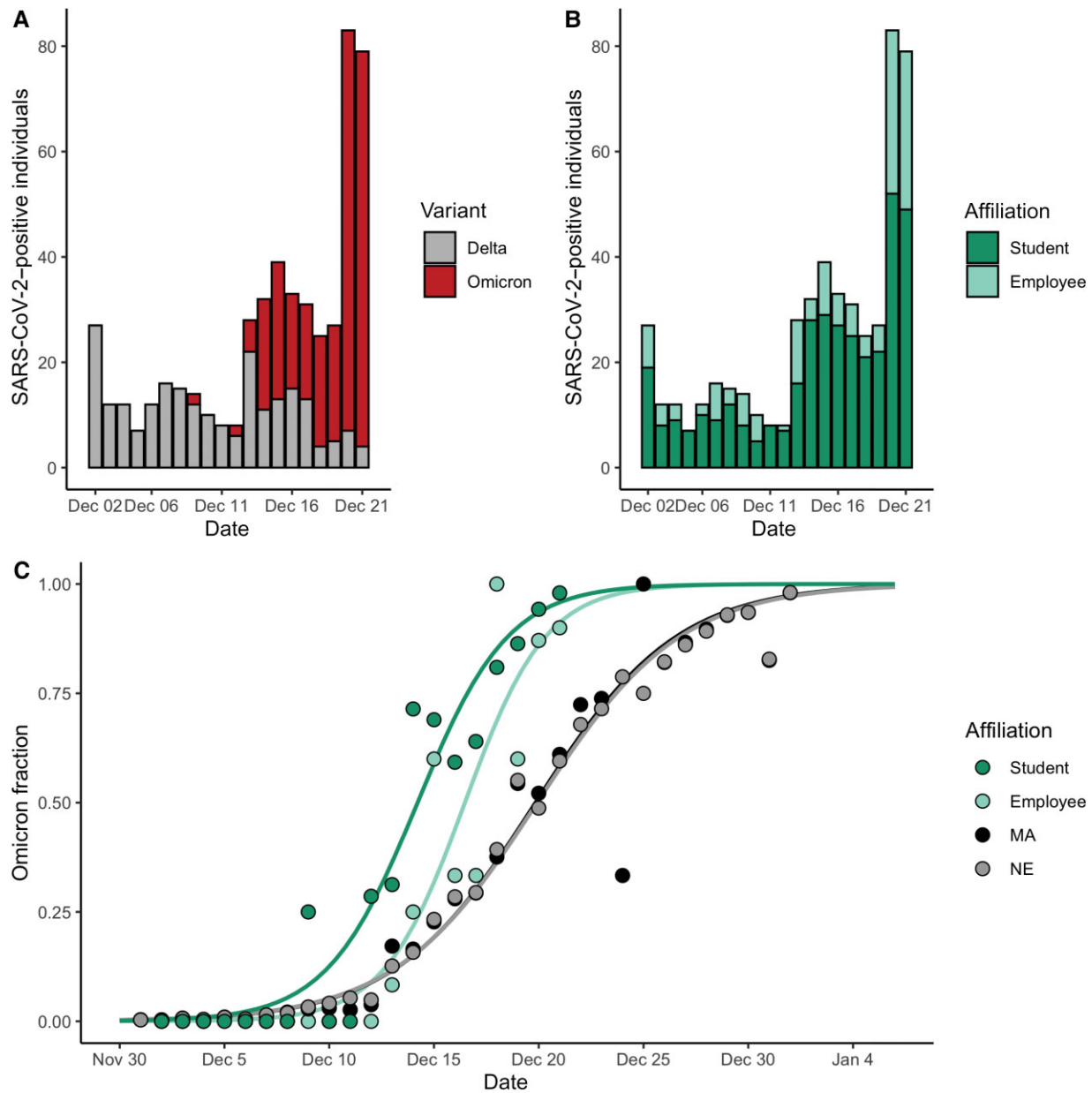


Figure 2. A, Total number of cases at Boston University (BU) stratified by variant and stacked from 2 December–21 December. Gray, Delta; red, Omicron. B, Total number of cases at BU stratified by affiliation status and stacked from 2 December–21 December. Light green, employees; green, students. C, Proportion of cases that were Omicron from 2 December–21 December (BU students and employees) and 1 December 1–1 January (MA). Data were modeled using logistic regression. Massachusetts data from Global Initiative on Sharing All Influenza Data. Abbreviations: MA, Massachusetts; NE, New England; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

through a vaccinated population means that even communities that escape the initial peak of Omicron in the United States require continued monitoring. For example, rural communities may experience late introductions of Omicron and may not notice its arrival until a significant proportion of the population has become infected. This is of particular concern in areas with low vaccination rates, where a rapid rise in case counts can overwhelm healthcare systems.

There are technical limitations to the generalizability of this study. SGTF, caused by the deletion of amino acids 69–70, was

one method we used for variant designation. While SGTF occurs in multiple SARS-CoV-2 variants, the Delta variant, which lacks this deletion, was the predominant circulating variant before Omicron's arrival. Thus, SGTF was sensitive and specific (94.6% and 99.5%, respectively, inferred from GISAID data [29–31]) for Omicron in MA during the study period. Moreover, while it is possible that differences in viral loads are confounded by differences in timing of viral incubation or clearance, longitudinal sampling of infected individuals suggests that Omicron samples have lower peak viral loads than

Table 3. Affiliation-Specific Point Estimates and 95% Confidence Intervals for O_x and for ΔO_{90-10}

Affiliation	O_{10}	O_{10} 95% CI	O_{50}	O_{50} 95% CI	O_{90}	O_{90} 95% CI	ΔO_{90-10} (days)	ΔO_{90-10} 95% CI (days)
Boston University employees	12 December	10–14 December	16 December	15–17 December	20 December	19–22 December	8.5	(7.9–9.1)
Boston University students	9 December	7–10 December	14 December	13–14 December	18 December	17–20 December	9.5	(9.1–9.9)
Massachusetts	12 December	12 December	19 December	19–20 December	27 December	27 December	14.8	(14.8–14.9)

^a O_x , the date at which the Omicron fraction equals x percent. ΔO_{90-10} , the duration of time that it takes the Omicron fraction to rise from 10% to 90%. CIs were generated via the Student t distribution, with estimation of the standard errors via the delta method (see the Methods section).

Abbreviation: CI, confidence interval.

Delta samples [36]. Finally, there are multiple potential models for the relationship between student and employee dynamics, including student–employee transmissions and transmissions that cycle between students, the community, and employees. However, we lack the viral genomic sequencing, contact tracing, and community testing data necessary to distinguish these possibilities.

Moreover, IHEs differ from MA in social structure and demographics, which may play a role in Omicron dynamics.

Though universities include individuals from different communities, the age distribution, residential life, and extracurricular activities could influence Omicron dynamics. Furthermore, the degree to which potential superspreader events could be important for the initial seeding of Omicron and its continued spread is not captured here. It is possible that the spread of Omicron in non-IHEs may be slower if the structure of the social network differs [43], resulting in fewer opportunities for clustered transmission. We cannot separate

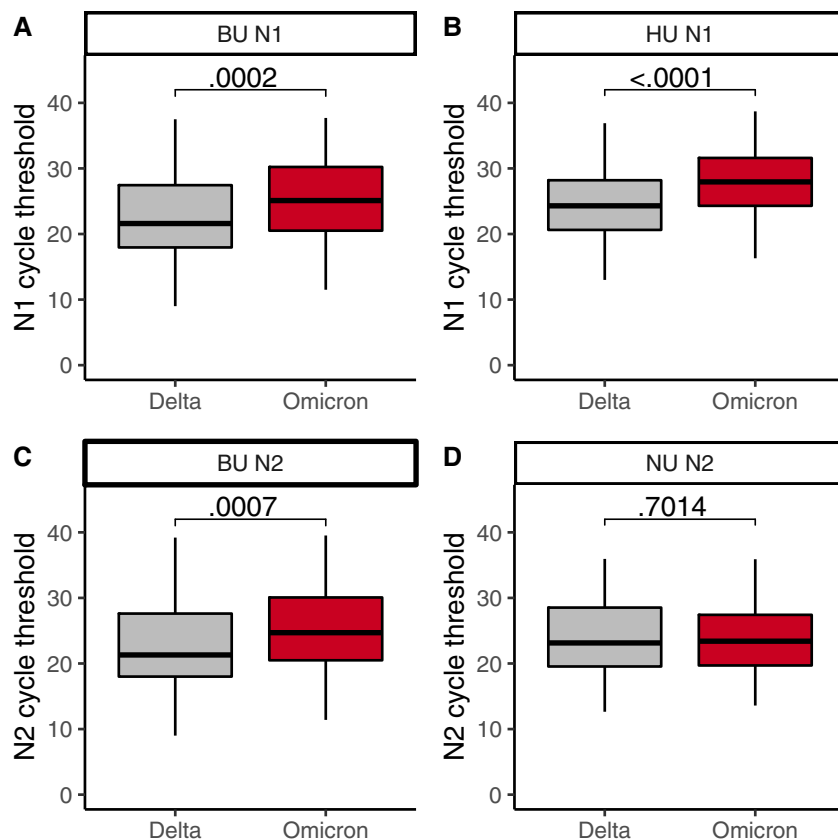


Figure 3. N1 cycle threshold for Delta vs Omicron cases at BU (A) and HU (B). N2 cycle threshold for Delta vs Omicron cases at BU (C) and NU (D). Gray, Delta; red, Omicron. The first, second, and third quartiles are within the box, with the median line bolded. The whisker length is 1.5 times the interquartile range (IQR), unless the furthest point is less than 1.5*(IQR) from the quartile. Outliers are displayed as points. P values via the Wilcoxon rank sum test and corrected via the Benjamini-Hochberg method (across the 4 comparisons in Figure 3 and the 1 comparison in Supplementary Figure 2). Abbreviations: BU, Boston University; HU, Harvard University; NU, Northeastern University.

possible sociobehavioral factors, such as an increase in indoor gatherings prior to the start of final examinations or in anticipation of the winter holidays, from properties intrinsic to the virus that may affect overdispersion. Finally, lower vaccination rates in MA may contribute to the relative fitness of Delta vs Omicron, and testing in MA may be biased if symptomatic testing occurs more frequently with Delta than with Omicron.

What can we learn from the spread of Omicron through universities that could help us mitigate future waves of SARS-CoV-2 or other pathogens? First, sites that have characteristics like IHEs can be informative early detection sites. We note 2 of many reasons. First, IHEs include individuals from a variety of backgrounds who intermix at the university and in the larger community, and IHEs have implemented university-wide asymptomatic screening programs. Screening programs like these can catch and categorize infections well before trends are noted in the larger community and have the potential to forecast testing needs and hospital admissions. Second, it is extremely difficult to stop the spread of a highly transmissible virus once it has become established in a community. BU, HU, and NU controlled the spread of previous variants of SARS-CoV-2 via a combination of high-cadence testing, isolation of positive individuals, contact tracing, quarantining of close contacts, social distancing, masking, vaccination requirements, and ventilation improvements. These measures were not sufficient to stop the spread of Omicron, and both BU and HU mitigated further spread via remote learning during the January term. This emphasizes the need for continued surveillance programs to rapidly identify and mitigate outbreaks before they become pandemics.

Supplementary Data

[Supplementary materials](#) are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. B. A. P. and J. T. accessed and verified the underlying data reported in the article. B. A. P. conducted statistical analyses, and L. F. W. and E. D. K. provided guidance for the analyses. B. A. P. and J. T. produced software and visualizations. J. T. collected and curated Boston University (BU) data, and L. D.-S., J. T. P., K. R. J., T. B., L. L., C. M. K., and D. H. H. provided assistance. N. L. W. collected and curated mCARMEN data with help from M. R. B., S. T. D., and T. G. N. Variant-specific polymerase chain reaction assay was collected and curated by M. C. and M. H. using custom primers and probes designed by M. S., M. G., D. T., and E. W. Project administration was aided by P. N. B. P. T. curated the Centers for Disease Control and Prevention (CDC) and Global Initiative on Sharing All Influenza Data (GISAID) data. J. R. A. and S. Y. collected and curated Northeastern University (NU) data. B. A. P. wrote the original draft of the manuscript with feedback provided by W. P. H., P. C. S., J. H. C., and M. S. The manuscript was reviewed and edited by N. L. W., P. N., K. R. J., T. B., W. P. H., P. C. S., J. H. C., and M. S. Authors W. P. H., P. C. S., J. H. C., and M. S. conceptualized and supervised the study and reviewed and edited the final manuscript.

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References

1. World Health Organization. Coronavirus (COVID-19) dashboard. Available at: <https://covid19.who.int>. Accessed 10 January 2022.
2. Centers for Disease Control and Prevention. COVID data tracker. 2020. Available at: <https://covid.cdc.gov/covid-data-tracker/>. Accessed 10 January 2022.
3. Brandal LT, MacDonald E, Veneti L, et al. Outbreak caused by the SARS-CoV-2 Omicron variant in Norway, November to December 2021. *Euro Surveill* 2021; 26:2101147.
4. Pulliam JRC, van Schalkwyk C, Govender N, et al. Increased risk of SARS-CoV-2 reinfection associated with emergence of the Omicron variant in South Africa. *bioRxiv* 2021.
5. Collie S, Champion J, Moultrie H, et al. Effectiveness of BNT162b2 vaccine against Omicron variant in South Africa. *N Engl J Med* 2021; 386(5):494–6.
6. Nemet I, Kliker L, Lustig Y, et al. Third BNT162b2 vaccination neutralization of SARS-CoV-2 Omicron infection. *N Engl J Med* 2021; 386(5):492–4.
7. Queen CS, Allen J. 100 U.S. colleges will require vaccinations to attend in-person classes in the fall. *The New York Times*. 2021; Available at: <https://www.nytimes.com/2021/04/29/us/colleges-vaccinations-enrollment.html>. Accessed 10 January 2022.
8. Frazier PI, Cashore JM, Duan N, et al. Modeling for COVID-19 college reopening decisions: Cornell, a case study. *Proc Natl Acad Sci U S A* 2022; 119.
9. Paltiel AD, Zheng A, Walensky RP. Assessment of SARS-CoV-2 screening strategies to permit the safe reopening of college campuses in the United States. *JAMA Netw Open* 2020; 3:e2016818.
10. Stubbs CW, Springer M, Thomas TS. The impacts of testing cadence, mode of instruction, and student density on fall 2020 covid-19 rates on campus. *medRxiv* 2020. Available at: <https://www.medrxiv.org/content/10.1101/2020.12.08.20244574v1.abstract>. Accessed 26 January 2022.
11. Hamer DH, White LF, Jenkins HE, et al. Assessment of a COVID-19 control plan on an urban university campus during a second wave of the pandemic. *JAMA Netw Open* 2021; 4:e2116425.
12. Valesano AL, Fitzsimmons WJ, Blair CN, et al. SARS-CoV-2 genomic surveillance reveals little spread from a large university campus to the surrounding community. *Open Forum Infect Dis* 2021; 8:ofab518.
13. COVID19 2021-12-17 update: Omicron variant. Available at: <https://tompkinscountynyny.gov/health/covid19-2021-12-17-update-omicron-variant>. Accessed 10 January 2022.
14. Covid-19 Information. COVID update—January remote learning and work. 2021. Available at: <https://www.harvard.edu/coronavirus/covid-update-january-remote-learning-work/>. Accessed 10 January 2022.
15. Stanford University. Update on the beginning of winter quarter. 2021. Available at: <https://news.stanford.edu/report/2021/12/16/first-two-weeks-winter-classes/>. Accessed 10 January 2022.
16. Hernandez J. Some colleges and universities will start the new year online as Omicron spreads. *NPR*. 2021. Available at: <https://www.npr.org/2021/12/22/1066788973/colleges-universities-remote-distance-learning-omicron>. Accessed 10 January 2022.
17. Vaccine booster. Available at: <https://www.northwestern.edu/coronavirus-covid-19-updates/health/vaccine/vaccine-booster.html>. Accessed 10 January 2022.
18. Callahan M. Northeastern requires booster vaccine shots for students, faculty, staff in the US. 2021. Available at: <https://news.northeastern.edu/2021/12/09/covid-vaccine-booster-requirement/>. Accessed 10 January 2022.
19. BU COVID-19 data dashboard. Available at: <https://www.bu.edu/healthway/community-dashboard/>. Accessed 24 January 2022.
20. Covid-19 Information. Harvard University-wide COVID-19 testing dashboard. Available at: <https://www.harvard.edu/coronavirus/testing-tracing/harvard-university-wide-covid-19-testing-dashboard/>. Accessed 24 January 2022.
21. Daily COVID-19 dashboard. 2021. Available at: <https://news.northeastern.edu/coronavirus/reopening/testing-dashboard/>. Accessed 24 January 2022.
22. Submission Number: EUA210677 Received: 12/20/2021 Applicant: The HFI Laboratory at Boston University Device: BU SARS-CoV-2 Test.
23. Emergency Use Authorization (EUA) Summary Queris SARS-CoV-2 Assay. 2021; Available at: <https://www.fda.gov/media/149445/download>. Accessed 26 January 2022.
24. Granato PA, Kimball SR, Alkins BR, et al. Comparative evaluation of the Thermo Fisher TaqPath TM COVID-19 Combo Kit with the Cepheid Xpert® Xpress SARS-CoV-2 Assay for detecting SARS-CoV-2 in nasopharyngeal specimens. 2021. Available at: <https://www.researchsquare.com/article/rs-429726/latest.pdf>. Accessed 26 January 2022.
25. Bouton TC, Lodi S, Turcinovic J, et al. Coronavirus disease 2019 vaccine impact on rates of severe acute respiratory syndrome coronavirus 2 cases and postvaccination strain sequences among health care workers at an urban academic medical center: a prospective cohort study. *Open Forum Infect Dis* 2021; 8:ofab465.
26. Welch NL, Zhu M, Hua C, et al. Multiplexed CRISPR-based microfluidic platform for clinical testing of respiratory viruses and SARS-CoV-2 variants. *bioRxiv* 2021. Available at: <http://medrxiv.org/lookup/doi/10.1101/2021.12.14.21267689>. Accessed 26 January 2022.
27. National Center for Immunization and Respiratory Diseases, Division of Viral Diseases. Science brief: Omicron (B.1.1.529) variant, CDC COVID-19 Science Briefs. Atlanta, GA: Centers for Disease Control and Prevention, 2021.
28. Centers for Disease Control and Prevention Case Task Force. United States COVID-19 cases and deaths by state over time. 2020. Available at: <https://data.cdc.gov/Case-Surveillance/United-States-COVID-19-Cases-and-Deaths-by-State-o/9mfq-cb36>. Accessed 21 January 2022.
29. Shu Y, McCauley J. GISAID: Global Initiative on Sharing All Influenza Data—from vision to reality. *Euro Surveill* 2017; 22.
30. Elbe S, Buckland-Merrett G. Data, disease and diplomacy: GISAID's innovative contribution to global health. *Glob Chall* 2017; 1:33–46.
31. Khare S, Gurry C, Freitas L, et al. GISAID's role in pandemic response. *China CDC Wkly* 2021; 3:1049–51.
32. Cox C. Fieller's theorem, the likelihood and the delta method. *Biometrics* 1990; 46:709–18.
33. Ver Hoef JM. Who invented the delta method? *Am Stat* 2012; 66:124–7.
34. US Census Bureau. 2020 census apportionment results. 2021. Available at: <https://www.census.gov/data/tables/2020/dec/2020-apportionment-data.html>. Accessed 22 January 2022.
35. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J R Stat Soc* 1995; 57:289–300.
36. Hay JA, Kissler SM, Fauver JR, et al. Viral dynamics and duration of PCR positivity of the SARS-CoV-2 Omicron variant. *bioRxiv* 2022.
37. Puhach O, Adea K, Hulo N, et al. Infectious viral load in unvaccinated and vaccinated patients infected with SARS-CoV-2 WT, Delta and Omicron. *bioRxiv* 2022.
38. Endo A. Centre for the Mathematical Modelling of Infectious Diseases COVID-19 Working Group, Abbott S, Kucharski AJ, Funk S. Estimating the overdispersion in COVID-19 transmission using outbreak sizes outside China. *Wellcome Open Res* 2020; 5:67.
39. Lloyd-Smith JO, Schreiber SJ, Kopp PE, Getz WM. Superspreading and the effect of individual variation on disease emergence. *Nature* 2005; 438:355–9.
40. Bi Q, Wu Y, Mei S, et al. Epidemiology and transmission of COVID-19 in 391 cases and 1286 of their close contacts in Shenzhen, China: a retrospective cohort study. *Lancet Infect Dis* 2020; 20:911–9.
41. Lee EC, Wada NI, Grabowski MK, Gurley ES, Lessler J. The engines of SARS-CoV-2 spread. *Science* 2020; 370:406–7.
42. Rocklöv J, Sjödin H, Wilder-Smith A. COVID-19 outbreak on the Diamond Princess cruise ship: estimating the epidemic potential and effectiveness of public health countermeasures. *J Travel Med* 2020; 27.
43. Boyer C, Rumlpler E, Kissler S, Lipsitch M. Infectious disease dynamics and restrictions on social gathering size. *bioRxiv* 2022.