Delta variants of SARS-CoV-2 cause significantly increased vaccine breakthrough COVID-19 cases in Houston, Texas

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NOTE: This preprint reports new research that has not been certified by peer review and should not be used to guide clinical practice.
Abstract

Genetic variants of SARS-CoV-2 have repeatedly altered the course of the COVID-19 pandemic, and disease in individual patients. Delta variants (B.1.617.2, AY.2, and AY.3) are now the focus of international concern because they are causing widespread COVID-19 disease globally. Vaccine breakthrough cases caused by SARS-CoV-2 variants also are of considerable public health and medical concern worldwide. As part of a comprehensive project, we sequenced the genomes of 4,920 SARS-CoV-2 from patient samples acquired March 15, 2021 through July 24, 2021 in the Houston Methodist hospital system and studied vaccine breakthrough cases. During the study period Delta variants increased to cause 94% of all COVID-19 cases and spread throughout the metropolitan Houston area. In addition, Delta variants caused a significantly higher rate of vaccine breakthrough cases (17.4% compared to 5.8% for all other variants). Importantly, only 8.4% of all COVID-19 cases occurred in fully vaccinated individuals, and relatively few of these patients required hospitalization. Individuals with vaccine breakthrough cases caused by Delta variants \( n = 194 \) had a low median PCR cycle threshold (Ct) value (a proxy for high virus load), and this value was not significantly different than the median Ct value observed in unvaccinated patients with COVID-19 caused by Delta variants. These data are consistent with the potential ability of fully vaccinated individuals to transmit SARS-CoV-2 to others. Our genomic and epidemiologic data emphasize that vaccines used in the United States are highly effective in decreasing severe COVID-19 disease, hospitalizations, and deaths.
Delta variants (B.1.617.2, AY.2, and AY.3) have become the focus of intense international concern because they are causing widespread COVID-19 disease in Southeast Asia, Europe, the United States, and elsewhere. For example, Delta has rapidly replaced the Alpha variant in the United Kingdom, previously the cause of virtually all COVID-19 cases in that country. Vaccine breakthrough cases caused by SARS-CoV-2 variants also have become of considerable public health and biomedical interest worldwide\textsuperscript{1-4}. To study Delta and vaccine breakthrough cases in metropolitan Houston, we sequenced the genomes of 4,920 SARS-CoV-2 from patient samples acquired March 15, 2021 through July 24, 2021 using an Illumina NovaSeq 6000 instrument\textsuperscript{5}. This period encompasses the time from initial identification of a Delta-related variant in our large Houston Methodist healthcare system until Delta variants became the supermajority (93.7%) of all new cases. The sample is 85% of the 5,756 cases of COVID-19 diagnosed in our health system during this period. Delta variants were identified based on genome sequence data as designated by Pangolin (https://cov-lineages.org/pangolin.html). During the study period 1,118 patients were diagnosed with Delta variants, and 414 of the 4,920 patients (8.4%) met the CDC definition of vaccine breakthrough cases (Table 1A). Breakthrough cases received either the Pfizer-BioNTech BNT162b2 ($n = 353$, 85%), Moderna mRNA-1273 ($n = 47$, 11%), or J&J/Janssen JNJ-78436735 ($n = 8$, 2%) vaccines, generally reflecting the supermajority of BNT162b2 vaccinations in our health system; vaccine type was not specified for six individuals. Fourteen patients with Delta Plus (Delta plus the K417N spike polymorphism) were identified, all diagnosed in July. Consistent with extensive
infections caused by Delta variants in Southeast Asia and elsewhere, several patients had very recent travel histories to countries with a high prevalence of these variants, suggesting acquisition abroad and importation into Houston. Patients with Delta variants were identified in 193 zip codes throughout the metropolitan area. Greater than 70 Delta subvariants were identified, likely reflecting the large population sizes and genetic diversity of Delta globally and in Houston and multiple introductions into the Houston metropolitan area. Patients infected with the same subvariant usually lived in different zip codes and had no apparent epidemiological link, consistent with the ability of Delta to spread very rapidly.

There is a considerable lack of detailed information about patients in the United States with COVID-19 caused by Delta variants. Compared to all other patients, Delta patients were not significantly different in median age or gender but did have a slight but significantly longer hospital length of stay (Table 1A). However, significantly fewer Delta patients required hospitalization and fewer required supplemental oxygen. Delta cases were more likely to be Caucasian or Asian (supporting the likelihood of multiple recent entry points) and less likely to be Hispanic or Latino, have significantly lower PCR cycle threshold (Ct) values (a proxy for higher virus load, a finding consistent with the reported increased transmissibility of Delta variants) on initial diagnosis, and cause a significantly higher rate of vaccine breakthrough cases (17.4% compared to 5.8% for all other variants) (Table 1A).

We next examined metadata for the 414 vaccine breakthrough cases (Table 1B). Vaccinated patients had a significantly higher Ct, likely indicating lower virus load on initial diagnosis. A significantly lower percentage of patients with Delta breakthrough
cases was admitted to hospital (Table 1B). Individuals with vaccine breakthrough cases caused by Delta variants \((n = 194)\) had a low median PCR cycle threshold (Ct) value (a proxy for high virus load), and this value was not significantly different than the median Ct value observed in unvaccinated patients with COVID-19 caused by Delta variants. On the presumption that there is a correlation between Ct value and live virus burden, these data are consistent with the potential ability of fully vaccinated individuals to transmit SARS-CoV-2 to others. Similarly, a high load of Delta in these two groups of patients may increase the possibility of generating additional variants with increased fitness, for example escape mutants that further circumvent host immunity.

Our genome sequence data coupled with patient metadata document a very rapid increase and spread of Delta variant cases in metropolitan Houston and a considerable corresponding decrease of COVID-19 cases caused by Alpha, findings similar to epidemiologic trends observed in the UK. Delta was significantly more likely to cause a vaccine breakthrough case (Table 1A). However, importantly, only 8.4% of all COVID-19 cases occurred in fully immunized individuals, and relatively few of these patients required hospitalization. In the aggregate, our data add critical new information to the finding that these three vaccines are highly efficacious in decreasing severe COVID-19 disease, hospitalizations, and deaths.

**Author Contributions:** Drs. Musser, Christensen, Olsen, and Long had full access to all study data and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Data acquisition, analysis, or interpretation of data: All authors

Drafting of the manuscript: All authors

Statistical analysis: Christensen

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Additional Information: Genome data used in this study have been deposited to GISAID.
References

1. Hacisuleyman E, Hale C, Saito Y, et al. Vaccine Breakthrough Infections with SARS-CoV-2 Variants. N Engl J Med 2021;384:2212-8.
2. Brosh-Nissimov T, Orenbuch-Harroch E, Chowers M, et al. BNT162b2 vaccine breakthrough: clinical characteristics of 152 fully-vaccinated hospitalized COVID-19 patients in Israel. Clin Microbiol Infect 2021.
3. COVID-19 Vaccine Breakthrough Infections Reported to CDC - United States, January 1-April 30, 2021. MMWR Morb Mortal Wkly Rep 2021;70:792-3.
4. Kustin T, Harel N, Finkel U, et al. Evidence for increased breakthrough rates of SARS-CoV-2 variants of concern in BNT162b2-mRNA-vaccinated individuals. Nat Med 2021.
5. Olsen RJ, Christensen PA, Long SW, et al. Trajectory of Growth of SARS-CoV-2 Variants in Houston, Texas, January through May 2021 Based on 12,476 Genome Sequences. medRxiv 2021:2021.05.20.21257552.
Table 1A. Summary of pertinent patient metadata for the 4,920 unique patients

| No. (%) with data | Delta Variant | Other Variants | Total | Statistical Analysis |
|-------------------|---------------|----------------|-------|----------------------|
|                  | 1118 (22.7%)  | 3802 (77.3%)   | 4920  |                      |

**Patient Characteristics**

|                        | Delta Variant | Other Variants | Total | Statistical Analysis |
|------------------------|---------------|----------------|-------|----------------------|
| Median Age (Years)     | 45.7          | 47.9           | 47.4  | $P=0.1026$ Mann-Whitney |
| Female                 | 594 (53.1%)   | 1979 (52.1%)   | 2573  (52.3%) | $P=0.5399$ Fisher's exact test |
| Male                   | 524 (46.9%)   | 1823 (47.9%)   | 2347  (47.7%) |                      |

**Ethnicity**

| Ethnicity            | Delta Variant | Other Variants | Total | Statistical Analysis |
|----------------------|---------------|----------------|-------|----------------------|
| Caucasian            | 486 (43.5%)   | 1485 (39.1%)   | 1971  (40.1%) | $P=0.0005$ Chi-square |
| Hispanic or Latino   | 273 (24.4%)   | 1160 (30.5%)   | 1433  (29.1%) |                      |
| Black                | 261 (23.3%)   | 886 (23.3%)    | 1147  (23.3%) |                      |
| Asian                | 51 (4.6%)     | 110 (2.9%)     | 161   (3.3%) |                      |
| Native American      | 3 (0.3%)      | 15 (0.4%)      | 18    (0.4%) |                      |
| Hawaiian/Pacific Islander | 3 (0.3%) | 5 (0.1%) | 8 (0.2%) |                      |
| Unavailable          | 35 (3.1%)     | 114 (3.0%)     | 149   (3.0%) |                      |

**BMI**

| Median BMI | Delta Variant | Other Variants | Total | Statistical Analysis |
|------------|---------------|----------------|-------|----------------------|
|            | 29.3          | 30.3           | 30.1  | $P<0.0001$ Mann-Whitney |

**Admission Data**

|                        | Delta Variant | Other Variants | Total | Statistical Analysis |
|------------------------|---------------|----------------|-------|----------------------|
| Admitted               | 457 (40.9%)   | 2075 (54.6%)   | 2532  (51.5%) | $P<0.0001$ Fisher's exact test |
| Not Admitted           | 661 (59.1%)   | 1727 (45.4%)   | 2388  (48.5%) |                      |
| Odds Ratio:            |               |                |       | 0.575 (95% CI 0.503 to 0.659) |
| Median LOS (Days)      | 5.3           | 5.0            | 5.0   | $P=0.0317$ Mann-Whitney |
### Max Respiratory Support

|                     | Alive  | Deceased |
|---------------------|--------|----------|
| Supplemental Oxygen | 4753 (96.6%) | 167 (3.4%) |
| Room Air            | 3650 (96.0%) | 152 (4.0%) |
| Mechanical Ventilation/ECMO | 1103 (98.7%) | 15 (1.3%) |
|                     | 438 (5.9%) | 169 (8.1%) |

**P < 0.0001**

Chi-square

### Mortality

|                     | Alive  | Deceased |
|---------------------|--------|----------|
| Alive               | 1103 (98.7%) | 15 (1.3%) |
| Deceased            | 4753 (96.6%) | 167 (3.4%) |

**P < 0.0001**

Fisher’s exact test

**Odds Ratio:**

0.327 (95% CI 0.194 to 0.558)

### Median PCR Cycle Threshold

|                     | Abbott Alinity | Hologic Panther |
|---------------------|----------------|-----------------|
|                     | 20.67 (n=413)  | 21.0 (n=105)    |
|                     | 25.74 (n=1375) | 25.75 (n=456)   |

**P < 0.0001**

Mann-Whitney

### Vaccine

|                      | No vaccine | >7 days past 1st vaccine | >14 days past 2nd vaccine |
|----------------------|------------|--------------------------|---------------------------|
| Alive                | 913 (81.7%)| 3444 (90.6%)              | 4357 (88.6%)              |
| Deceased             | 11 (1.0%)  | 138 (3.6%)                | 149 (3.0%)                |
|                      | 194 (17.4%)| 220 (5.8%)                | 414 (8.4%)                |

**P < 0.0001**

Chi-square

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Data include 4,920 unique patients with high-quality sequence results between March 15, 2021, and July 24, 2021.

BMI: body mass index; CI: confidence interval; ECMO: extracorporeal membrane oxygenation; LOS: length of stay
Table 1B. Summary of pertinent patient metadata for the 414 fully vaccinated patients

|                                | Vaccinated | Not Vaccinated | Total       | Statistical Analysis |
|--------------------------------|------------|---------------|-------------|----------------------|
| **Median PCR Cycle Threshold** |            |               |             |                      |
| Abbott Alinity                 | 27.03      | 24.09         | n = 1788    | P=0.0080 Mann-Whitney |
| n = 190                        |            | n = 1598      |             |                      |
| Hologic Panther                | 27.35      | 24.5          | n = 561     | P=0.0767 Mann-Whitney |
| n = 48                         |            | n = 513       |             |                      |
| **Median PCR Cycle Threshold (Delta variant only)** |            |               |             |                      |
| Abbott Alinity                 | 20.67      | 20.67         | n = 413     | P=0.9231 Mann-Whitney |
| n = 87                         |            | n = 326       |             |                      |
| Hologic Panther                | 20.60      | 21.1          | n = 105     | P=0.9514 Mann-Whitney |
| n = 17                         |            | n = 88        |             |                      |
| **Median PCR Cycle Threshold (Non-Delta only)** |            |               |             |                      |
| Abbott Alinity                 | 35.77      | 25.31         | n = 1375    | P<0.0001 Mann-Whitney |
| n = 103                        |            | n = 1272      |             |                      |
| Hologic Panther                | 35.5       | 25.5          | n = 456     | P=0.0017 Mann-Whitney |
| n = 31                         |            | n = 425       |             |                      |
| **Admission Data**             |            |               |             |                      |
| Admitted                       | 147 (35.5%) | 2385 (52.9%)   | 2532 (51.5%) | P<0.0001 Fisher’s exact test |
| Not Admitted                   | 267 (64.5%) | 2121 (47.1%)   | 2388 (48.5%) | Odds Ratio: 0.490 (95% CI 0.396 to 0.602) |
|                          | Delta Variant | Other Variants | Total |
|--------------------------|---------------|----------------|-------|
| **No. (%) with data**    | 194 (46.9%)   | 220 (53.1%)    | 414   |
| **Cancer History**       |               |                |       |
| Yes                      | 22 (11.3%)    | 27 (12.3%)     | 49 (11.8%) |
|                          | **P=0.8790**  |                |       |
| No                       | 172 (88.7%)   | 193 (87.7%)    | 365 (88.2%) |
|                          | Fisher’s exact test |                |       |
|                          | Odds Ratio:   |                |       |
|                          | 0.914 (95% CI 0.508 to 1.677) | |       |
| **Admission Data**       |               |                |       |
| Admitted                 | 56 (28.9%)    | 91 (41.4%)     | 147 (35.5%) |
|                          | **P=0.010**   |                |       |
| Not Admitted             | 138 (71.1%)   | 129 (58.6%)    | 267 (64.5%) |
|                          | Fisher’s exact test |                |       |
|                          | Odds Ratio:   |                |       |
|                          | 0.575 (95% CI 0.384 to 0.866) | |       |