Rapid displacement of SARS-CoV-2 variant B.1.1.7 by B.1.617.2 and P.1 in the United States

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Abstract

The SARS-CoV-2 variant of concern B.1.617.2 displaced B.1.1.7 as the dominant variant in England and other countries. This study aimed to determine whether B.1.617.2 was also displacing B.1.1.7 in the United States. We analyzed PCR testing results and viral sequencing results of samples collected across the United States, and showed that B.1.1.7 was rapidly being displaced and is no longer responsible for the majority of new cases. The percentage of SARS-CoV-2 positive cases that are B.1.1.7 dropped from 70% in April 2021 to 42% in just 6 weeks. Our analysis showed rapid growth of variants B.1.617.2 and P.1 as the primary drivers for this displacement. Currently, the growth rate of B.1.617.2 was higher than P.1 in the US (0.61 vs. 0.22), which is consistent with reports from other countries. Lastly, we showed that B.1.617.2 was growing faster in counties with a lower vaccination rate.

Introduction

The SARS-CoV-2 B.1.617.2 variant, also named Delta, has recently been classified as a variant of concern (VOC) by Public Health England (PHE), the World Health Organization (WHO), and the U.S. Centers for Disease Control (CDC) [1]. The B.1.617.2 variant is the predominant variant in India and in the United Kingdom, and has been identified in 65 countries as of June 17, 2021 [2]. It has been shown to be more transmissible than the SARS-CoV-2 B.1.1.7 variant, also named the Alpha variant, in England [3]. Moreover, a study by Public Health England showed that vaccine efficacy for AstraZeneca and Pfizer vaccines remained very good (>90%) against hospitalizations after two doses [4]. However, vaccine efficacy was lower against B.1.617.2 compared to B.1.1.7 after one dose.

In the United States, the first sequence of B.1.617.2 was identified on March 16. The context in the United States is different compared to England in terms of vaccine strategies and the existing viral background. In England, B.1.1.7 represented more than 90% of the SARS-CoV-2 sequences when B.1.617.2 was first identified in the country, and there were very few sequences of P.1, also named Gamma, another variant of concern. In the United States, B.1.1.7 plateaued just above 70%, and there was a greater diversity of variants when B.1.617.2 started to emerge, including an increasing amount of P.1 [2].

The objectives of this study are therefore (i) to analyze the impact of the introductions of B.1.617.2 and P.1 variants of concern on the prevalence of B.1.1.7 in the United States, and (ii) to analyze the growth and transmissibility of B.1.617.2 and P.1 in the United States. To this end, we looked at the PCR testing results and sequencing results of samples collected by the Helix laboratory across the United States since April 2021. Importantly, the collection method and collection sites have not changed in the last few months, and the samples analyzed should not be biased for very localized outbreaks. We therefore make the assumption that there was no significant sampling bias between the testing and sequencing done by our lab in February and March 2021, when B.1.1.7 was rapidly increasing in the United States, and the months of May and June 2021.

Methods

Ethical statement

Helix data analyzed and presented here were obtained through IRB protocol WIRB#20203438, which grants a waiver of consent for a limited dataset for the purposes of public health under section 164.512(b) of the Privacy Rule (45 CFR § 164.512(b)).

Helix COVID-19 test data and sample selection

All viral samples in this investigation were collected by Helix through its COVID-19 diagnostic testing laboratory. The Helix COVID-19 Test (EUA 201636) was run on specimens collected across the US, and results were obtained as part of our standard test processing workflow using specimens from anterior nares swabs. The Helix COVID-19 Test is based on the Thermo Fisher TaqPath COVID-19 Combo Kit, which targets three SARS-CoV-2 viral regions (N gene, S gene, and ORF1ab). Test results from positive cases, together with a limited amount of metadata (including sample collection date, state, and RT-qPCR Cq values for all gene targets), were used to build the research database used here. Ongoing summary level data are viewable at https://www.helix.com/covid19db. Data used for analysis are based on samples that tested positive with N gene Cq value < 29.

Viral lineage designation

For non-SGTF samples, we rely on sequencing followed by the assignment of a Pango lineage [5] using pangolearn (https://github.com/cov-lineages/pangoLEARN) to calculate the frequencies of viral variants. Because we do not sequence every positive sample, our resolution for non-SGTF variants is more coarse than for B.1.1.7: in contrast to the SGTF data, there were only 19,987 samples for which we have sequences -- and therefore Pango lineages -- for the period covered by this analysis. This coarser resolution is particularly evident in more recent data, due to the variable turn-around time for sequencing. Sequencing was performed by Illumina [6], and more recently by Helix, as part of the SARS-CoV-2 genomic surveillance program led by the Centers for Disease Control and Prevention (CDC).

Vaccination rates

Vaccination rate by county was downloaded from the CDC (https://covid.cdc.gov/covid-data-tracker/#county-view). The percent of individuals completely vaccinated on the given date was used. We used the percentage of individuals completely vaccinated as of May 1 2021, a date that would be relevant to the types of virus growth patterns seen in June.

Results

B.1.1.7 is rapidly decreasing in the US

One of the defining mutations of the B.1.1.7 variant of concern is the deletion of amino acids 69 and 70 in the spike protein. This deletion interferes with the PCR test target on the S gene in many COVID-19 tests [7], including the Helix COVID-19 Test, and causes S-gene target failure (SGTF). In January 2021, SGTF positives were found to be caused by B.1.1.7 variants, as well as a few other variants such as B.1.375. Moreover, the S-gene target may fail if viral load is low and Cq is high, usually above 30. To assess whether SGTF could be used to study the increase or decrease of the B.1.1.7 variant of concern in the United States, we looked at all 4,562 sequences from SGTF samples in May and June 2021. Of those, 99.3% (4,532 of 4,562) were B.1.1.7 (**Figure 1A**). The next lineage leading to SGTF in that time period in the United States was B.1.525 (10 of 4,562). Of note, one and only one of the SGTF samples sequenced was a P.1 variant. The other P.1 variants sequenced, as well as all other variants of concerns that are not B.1.1.7, did not lead to SGTF. SGTF is therefore a reliable test to look at the epidemiological dynamics of B.1.1.7 in the United States.

We therefore analyzed 243,769 positive samples for SARS-CoV-2 with a Cq for the N gene <29. All of these samples were tested at the Helix laboratory between January 1 and June 15 2021. These samples were collected across the United States, but they do not proportionally represent the different areas of the United States by population, and a large fraction of them come from Florida (25.7%). The other states that are most represented in this study are: California, Pennsylvania, Georgia, North Carolina, and Michigan. Both SGTF and sequencing data indicate that the B.1.1.7 variant, after becoming the dominant SARS-CoV-2 lineage in the United States [6,8] has seen its prevalence plateau at around 70% in April 2021, with a maximum at 71.1% on April 25, 2021. By looking at May and June test results in the US, we see a clear and rapid decrease of the fraction of SGTF among positive results, decreasing from 69.6% on April 26-30 (3,826 of 5,499) to 42% on June 11-15 (400 of 952) (**Figure 1B**). To make sure that this result was not driven by a change in the states or regions with high number of cases, or other artefacts, we looked at the trend in Florida alone and observed the same rapid displacement (**Figure 1C**). Overall, these results show that the variant of concern B.1.1.7 is rapidly being displaced in the United States.

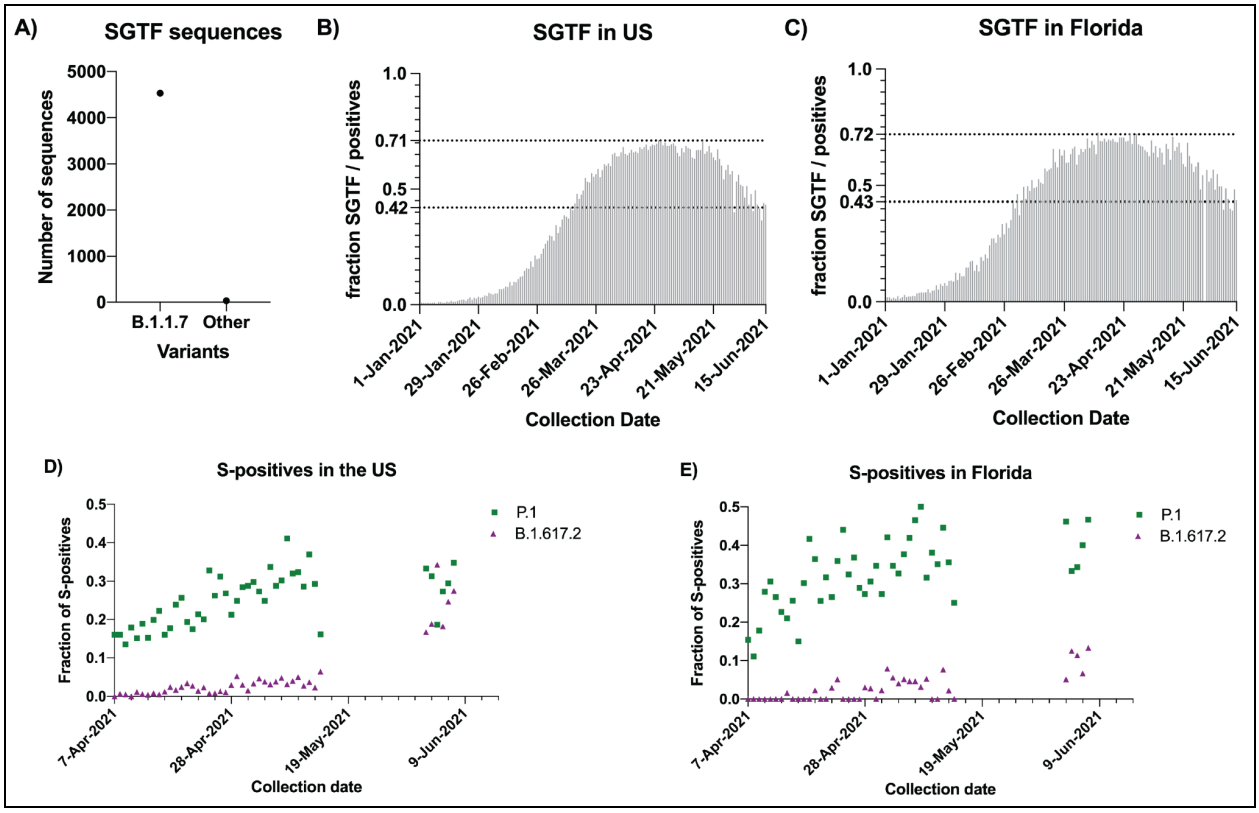


Figure 1: B.1.1.7 is being replaced by B.1.617.2 and P.1 in the United States. A) Counts of S-Gene Target Failure (SGTF) sequenced in May and June 2021 that were B.1.1.7 or Other variants. B) Fraction of SGTF to total positives per day in the US. The two dotted lines correspond to the maximum level observed in the US (71%) and the current level (42%). C) Fraction of SGTF to total positives per day in Florida. The two dotted lines correspond to the maximum level observed in Florida (72%) and the current level (43%). D) Fraction of S-positives sequenced that were either B.1.617.2 (purple triangles) or P.1 (green squares) by day in the US. No sequences were available from May 14 to June 2 2021. E) Fraction of S-positives sequenced that were either B.1.617.2 (purple triangles) or P.1 (green squares) by day in the US.

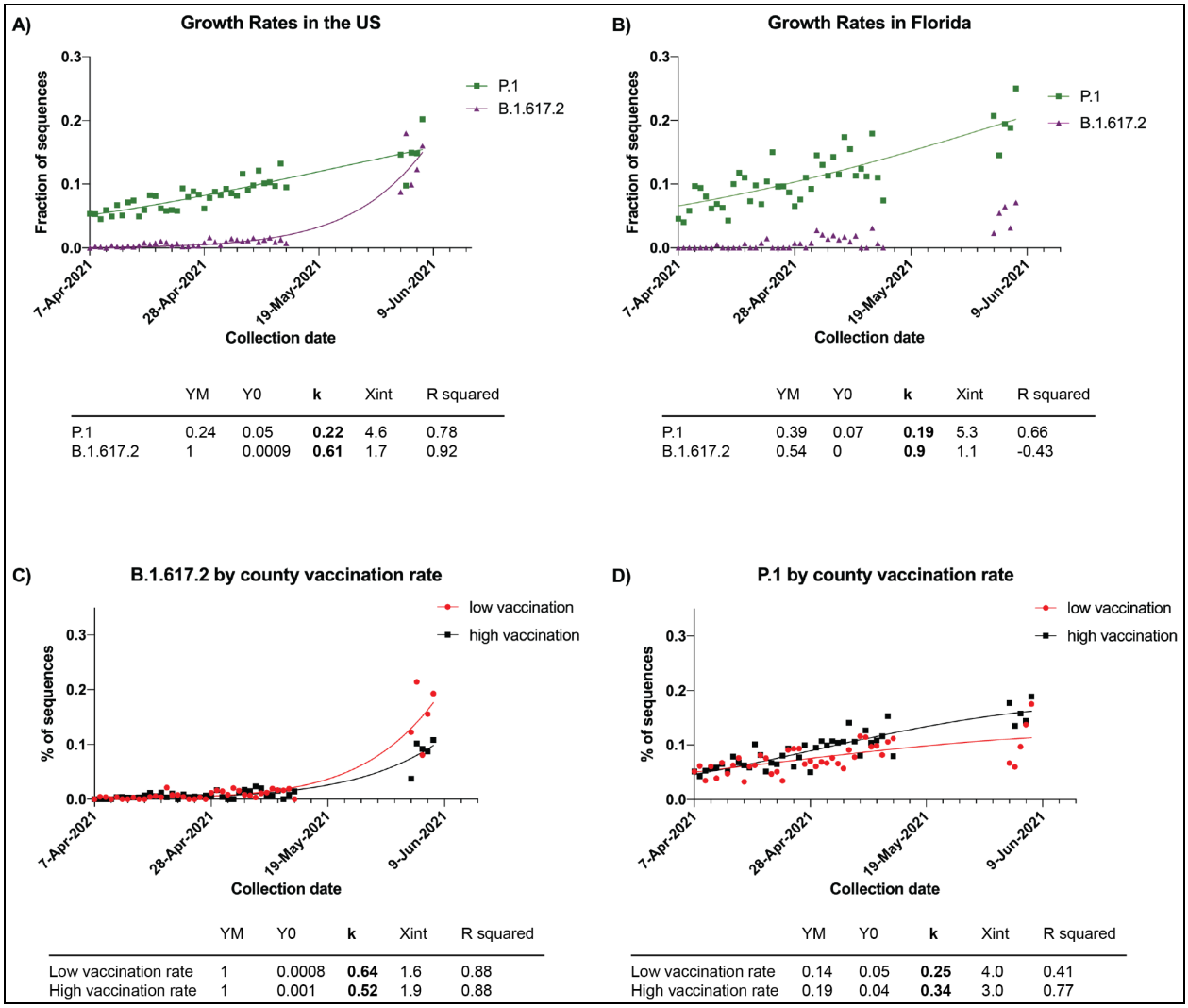
B.1.617.2 and P.1 are responsible for B.1.1.7 decrease

We analyzed the Pango lineage associated with each sequence to investigate which variants might be displacing B.1.1.7 in the United States. Since SGTF is a near perfect proxy for B.1.1.7, we first looked at what variants comprised the growing S-positive fraction (the non-SGTF). We sequenced 353 samples that were S-positives and collected from June 2 to June 8, when the B.1.1.7 fraction was decreasing rapidly. P.1 represented 28% and B.1.617.2 represented 24.6% of S-positive samples in the United States (**Figure 1D**), and this fraction is increasing. By looking at the SGTF results, we observed that for the week from June 9 to June 15, S-positives represented 57.1% of the positives (800 of 1,401). Using the proportion of S-positives from the week prior, we estimate that P.1 represented at least 16% and B.1.617.2 represented at least 14% of the cases in the US for the week of June 9 to June 15. In our more targeted look at Florida, the overall proportion of S-positives explained by P.1 and B.1.617.2 is similar to

nationwide (50%). However, the proportion explained by each variant was different from nationwide: P.1 represented 40.6% (65 of 160) of the S-positives, while B.1.617.2 represented 9.4% (15 of 160) of them (**Figure 1E**). Overall, these results showed that the main variants replacing B.1.1.7 in the United States are the two variants of concern P.1 and B.1.617.2. As of early June 2021, our data showed that the proportion of S-positives that are P.1 vs. B.1.617.2 differed between states.

Growth rates of B.1.617.2 and P.1 in the United States

Our observation that both P.1 and B.1.617.2 are contributing to the displacement of B.1.1.7 in the United States stands in contrast to what was observed in England, where B.1.617.2 was the main variant replacing B.1.1.7. To better understand the dynamics between these two new variants of concern and B.1.1.7, we looked at growth rates by fitting a logistic growth curve on the fraction of all positives that are P.1 or B.1.617.2. In the United States, this analysis showed that the growth rate of B.1.617.2 was faster than P.1 ($k = 0.61$ vs. 0.22), and that the predicted maximum fraction of B.1.617.2 was higher than P.1 (**Figure 2A**). While the numbers obtained In Florida confirm this analysis, it was also evident that the number of B.1.617.2 in Florida was still too low to make accurate predictions (**Figure 2B**).



	YM	Y0	k	Xint	R squared
P.1	0.24	0.05	**0.22**	4.6	0.78
B.1.617.2	1	0.0009	**0.61**	1.7	0.92

	YM	Y0	k	Xint	R squared
P.1	0.39	0.07	**0.19**	5.3	0.66
B.1.617.2	0.54	0	**0.9**	1.1	-0.43

	YM	Y0	k	Xint	R squared
Low vaccination rate	1	0.0008	**0.64**	1.6	0.88
High vaccination rate	1	0.001	**0.52**	1.9	0.88

	YM	Y0	k	Xint	R squared
Low vaccination rate	0.14	0.05	**0.25**	4.0	0.41
High vaccination rate	0.19	0.04	**0.34**	3.0	0.77

Figure 2: Growth rates of B.1.617.2 and P.1 in the United States. A) and B) Fractions of total sequences (SGTF or not) by day in the US (panel A) and in Florida (panel B) that were B.1.617.2 (purple triangle) or P.1 (green squares). A logistic growth curve was then fitted and is represented by the continuous purple line for B.1.617.2 and green line for P.1 The table below the graphs shows the key values of the curve Y=YM*Y0/((YM-Y0)*exp(-k*x) +Y0). YM is the maximum population; Y0 is the starting population; k is the rate constant. R squared is a measure of the goodness of fit. C) and D) Growth curves of B.1.617.2 (panel C) and P.1 (panel D) by county vaccination rate. Red represents counties with a low vaccination rate (below 28.5% completely vaccinated on May 1). Black represents counties with a high vaccination rate (above 28.5% completely vaccinated on May 1). Each symbol indicates the fraction of B.1.617.2 or P.1 to the number of samples sequenced per day. Characteristics of the curves are below each panel.

The growth rates of B.1.617.2 and P.1 differ by county vaccination rate

The samples sequenced at Helix since April 2021 have spanned 747 US counties. We compared the sequence data from these counties to county vaccination rates reported by the CDC. Of the 19,987 samples sequenced during the study period, we divided them roughly evenly into those from counties with lower vaccination rates (<28.5% completely vaccinated on May 1: 10,104 samples across 455 counties) and those with higher vaccination rates (9,883 samples across 292 counties). The growth curve for B.1.617.2, which is more transmissible but against which vaccines are highly effective, shows faster growth in counties with lower vaccination rates (**Figure 2C**). In contrast, P.1, which is less transmissible but against which vaccines have somewhat less efficacy, has a higher prevalence in counties with higher vaccination rates (**Figure 2D**).

Discussion

Here, we use viral sequence data from 19,987 Helix COVID-19 tests collected since April 2021 and 243,769 SGTF values from Helix COVID-19 tests collected since January 2021 to show the trajectories of different variants of concern in the United States. The total percentage of positive COVID-19 tests attributed to B.1.1.7 in the United States fell from a peak of 70% in April down to 42% in just 6 weeks. We show that most of the displacement of B.1.1.7 can be attributed to B.1.617.2 and P.1. Both of these variants of concern are growing in the United States and explain the rapid proportional decrease of the B.1.1.7 variant. Preliminary growth rates show that both B.1.617.2 and P.1 are growing faster than B.1.1.7, and that B.1.617.2 is growing faster than P.1 in the United States (k= 0.61 vs. k=0.22). Our results are consistent with those from Public Health England, which found that compared to B.1.1.7, B.1.617.2 had a growth rate of 0.93 and P.1 had a growth rate of 0.34 [3].

The expectation is that B.1.617.2 will soon be the dominant variant in the United States. However, questions remain whether it will entirely take over as it is doing in England, or whether it will plateau at a lower level like B.1.1.7 did in the US. One reason to argue that B.1.617.2 may not reach levels as high in the US compared to England is the more diverse sets of policies between US states with regard to vaccinations and other public health measures. With this in mind, we showed that B.1.617.2 is growing more rapidly in counties with lower vaccination rates (**Figure 2C and 2D**).

One important limitation to this study is the relatively small number of positives analyzed in the last 2 months. This is partly due to the much lower number of cases in the United States and the decrease in test positivity rate. Another limitation is that the data is not homogeneous across the United States. We will continue to test and sequence positive samples in order to characterize these variants. We also continuously update our public dashboard tracking SGTF and sequences by state and collection date at https://public.tableau.com/profile/helix6052#!/.

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Declarations of Interest

A.B., E.T.C., S.L., S.W., T.C., S.J., J.N., J.M.R., E.S., X.W., D.W., D.B., M.L., J.T.L., M.I., N.L.W. and W.L. are employees of Helix.

References

1. CDC. SARS-CoV-2 Variant Classifications and Definitions. https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-info.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fcases-updates%2Fvariant-surveillance%2Fvariant-info.html (2021).
2. outbreak.info. https://outbreak.info/situation-reports?pango=B.1.617.2&loc=IND&loc=GBR&loc=USA&selected=IND.
3. Public Health England. Investigation of SARS-CoV-2 variants of concern: technical briefings. https://www.gov.uk/government/publications/investigation-of-novel-sars-cov-2-variant-variant-of-concern-20201201 (2020).
4. Public library. https://khub.net/web/phe-national/public-library/-/document_library/v2WsRK3ZlEig/view/479607266.
5. Rambaut, A. *et al.* A dynamic nomenclature proposal for SARS-CoV-2 lineages to assist genomic epidemiology. *Nat Microbiol* **5**, 1403–1407 (2020).
6. Washington, N. L. *et al.* Emergence and rapid transmission of SARS-CoV-2 B.1.1.7 in the United States. *Cell* **184**, 2587–2594.e7 (2021).
7. Bal, A. *et al.* Two-step strategy for the identification of SARS-CoV-2 variant of concern 202012/01 and other variants with spike deletion H69-V70, France, August to December 2020. *Euro Surveill.* **26**, (2021).
8. Alpert, T. *et al.* Early introductions and transmission of SARS-CoV-2 variant B.1.1.7 in the United States. *Cell* **184**, 2595–2604.e13 (2021).