UK Health Security Agency

SARS-CoV-2 therapeutics technical briefing 2

Genomic surveillance

3 March 2022

This report provides an update on previous briefings up to 21 January 2022

Contents

The technical briefings on the SARS-CoV-2 variants are published on GOV.UK

1. Summary

The UK Health Security Agency's (UKHSA) coronavirus (COVID-19) therapeutics programme of work aims to support rapid deployment of specific COVID-19 therapeutics including neutralising monoclonal antibodies (nMABs) and antivirals (AVs) by undertaking genomic, virological, and epidemiologic surveillance. This report is produced to share genomic surveillance information with partner organisations.

Clinical access policies for the use of nMABs and AVs for the United Kingdom (UK) are published via the therapeutic central alert system (CAS alerts), following agreement by the Chief Medical Officer. The latest COVID-19 therapeutic access policies can be found at CAS – Coronavirus (COVID-19) Alerts (mhra.gov.uk).

Remdesivir (Veklury®) has been available to patients hospitalised due to COVID-19 since May 2020. More recently remdesivir has been available to patients with hospital onset COVID-19 infection and to non-hospitalised individuals at highest risk with COVID-19 infection. Casirivimab/imdevimab (Ronapreve®) has been in clinical use for inpatients since September 2021 and was briefly available as a treatment for non-hospitalised patients, but currently remains in very limited use for individuals admitted due to COVID-19 with confirmed Delta infection. Sotrovimab (Xevudy®) has been in use since mid-December 2021 in both the non-hospitalised at highest risk and the hospital-onset COVID-19 cohorts and is also being studied in admitted patients within the RECOVERY trial. Molnupiravir (Lagevrio®) has been in clinical use in non-hospitalised patients at highest risk since mid-December 2021 and in those with hospital onset COVID-19 since early-February 2022; molnupiravir is also being studied for its effectiveness as a community treatment, through the PANORAMIC trial, in individuals over 50 years and all age groups with at least one risk factor for hospitalisation. Nirmatrelvir plus ritonavir (Paxlovid®) is now available to both non-hospitalised patients at highest risk and those with hospital-onset COVID-19 infection.

Surveillance sampling is described in the interim genomic surveillance protocol for inpatient settings and is currently being updated in line with the changing clinical policy and to encompass community settings. Detailed variant surveillance analysis is published in the SARS-CoV-2 variant technical briefings. Analyses are experimental and findings will have a high level of uncertainty.

Unless stated otherwise, this technical briefing uses a data cut-off of 15 February 2022 to allow time for analyses. Nirmatrelvir plus ritonavir analyses will be included in the next therapeutics technical briefing.

UK genomic dataset mutation scanning

BA.1

Of the acquired spike mutations (additional to those mutations that define the lineage) occurring at over 1% prevalence in BA.1, R346K is at a predicted contact residue site for sotrovimab. The other mutations over 1% are L5F, L452R, F643L, Q628K, A701V, and I1081V. There are no mutations observed in non-structural proteins 10, 12 and 14 (NSP 10-14) at contact residue sites associated with remdesivir or molnupiravir.

BA.2

There are no acquired spike mutations occurring at over 1% prevalence in BA.2. There are no mutations observed in NSP 10-14 at contact residue sites associated with remdesivir or molnupiravir.

Post treatment viral sequences

Six residues displayed a change in post-treatment sequences compared to pre-treatment sequences, suggesting possible evidence of selection: S:132D/Q and S:G446V in patients infected with Delta and treated with casirivimab and imdevimab; N211S, S:P337L/R/S/ and S:E340A/D/K in patients infected with Omicron and treated with sotrovimab; and NSP14:V394A in patients infected with Delta and treated with remdesivir. Some of these residues are known contact residues for the treatment agent used. The mutation S:N211S is an alignment artefact caused by a deletion at this position in Omicron.

The working hypothesis is that these mutations detected post treatment may have helped the virus to escape from the treatment agent used to some extent. The mutations are not detected widely in circulating SARS-COV-2 at the moment and so are not judged to pose a current clinical treatment concern. They now require assessment through structural modelling and laboratory testing to confirm this hypothesis, and their prevalence in the population will also be closely monitored.

2. Genomic surveillance analyses

For the purpose of this analysis, as of 15 February 2022, 83.09% of sequences were BA.1, 16.03% were from BA.2, and 0.89% were from other lineages. The latest data for the prevalence of different variants amongst sequenced episodes is presented in Technical Briefing 37. BA.2 rarely contains the spike gene deletion at position 69-70 and is S-gene target positive (SGTP) on polymerase chain reaction (PCR) diagnostic assays with targets in this area. SGTP is now a reasonable proxy for BA.2, accounting for 97% of sequenced SGTP cases with an increasing trend. Sequencing data linked to data on prescriptions is complete up to 14 February 2022.

Genomic surveillance analyses utilise information on residues which are involved in drug binding. These residues of interest have been identified by selecting structural models of SARS-CoV-2 proteins of interest in complex with either therapeutic antibodies or small molecule inhibitors, as described in the first Therapeutics technical briefing. Mutations at residues of interest are hypothesised to predict changes in drug-virus complexes, providing preliminary data on the potential phenotypic effects of mutations. Of note, residues on the spike gene are monitored with respect to casirivimab, imdevimab, and sotrovimab. Contact residue sites in NSP10, 12 and 14 are monitored with respect to molnupiravir and remdesivir and residue sites in NSP5 will be monitored with respect to nirmatrelvir plus ritonavir.

VOC-21NOV-01 (Omicron BA.1)

Of the lineage defining spike mutations in BA.1, N440K is at a predicted contact residue site for sotrovimab. The acquired spike mutations occurring at over 1% prevalence in BA.1 between the 7 and 14 of February are L5F, R346K, L452R, F643L, Q628K, A701V, and I1081V. R346K is the lineage defining mutation for BA.1.1 (a sub-lineage of BA.1) representing 27.74% of BA.1 samples between 22 November 2021 and 14 February 2022 and is a predicted contact residue site for sotrovimab.

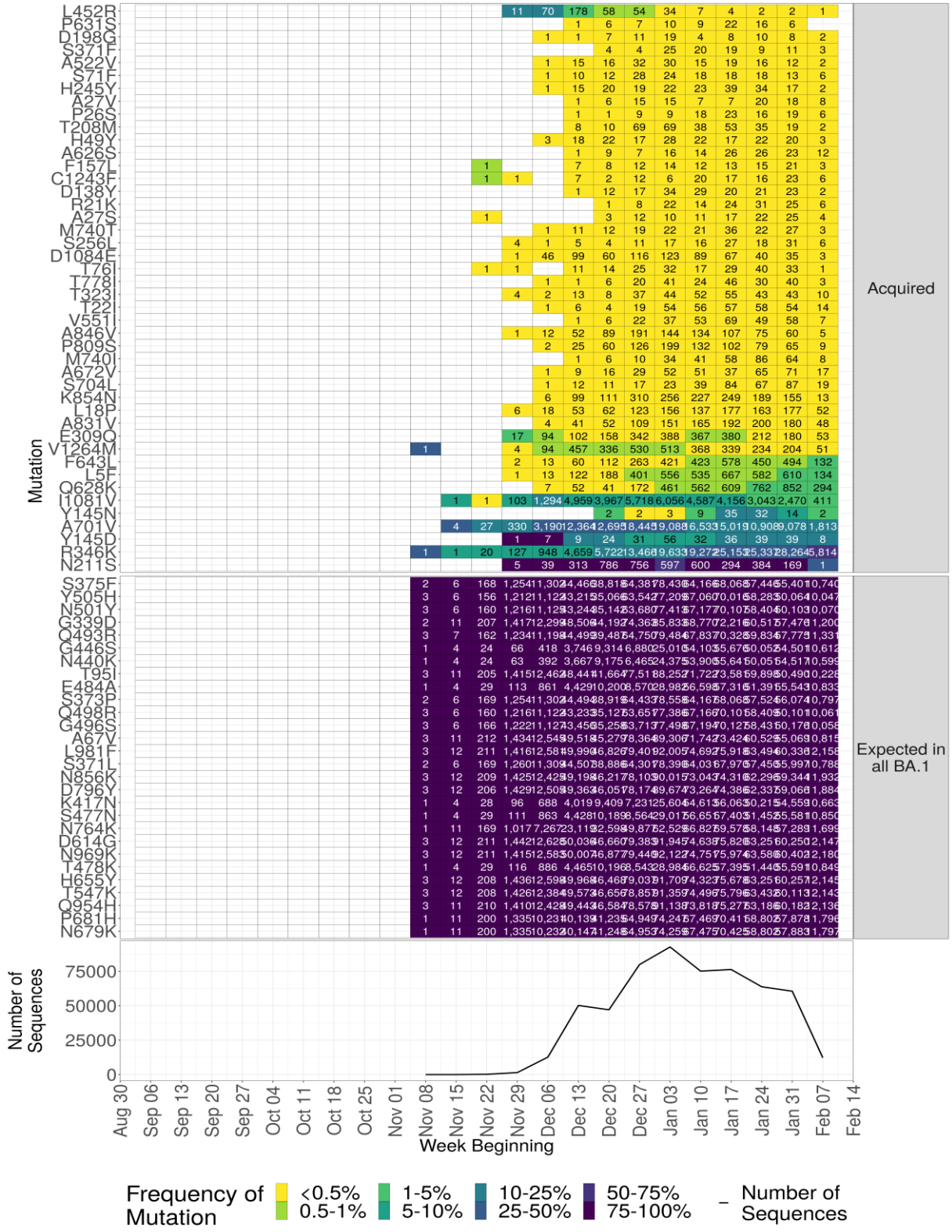
The NSP12 mutations occurring at over 1% prevalence between 7 and 14 February are G44S, D153Y, I223V, T226M, and Q875R. There are no mutations observed in NSP12 at contact residue sites associated with remdesivir or molnupiravir. In BA.1 no acquired mutations were present for NSP10 or NSP14 in proportions greater than 1%.

VUI-22JAN-01 (Omicron BA.2)

Of the lineage defining spike mutations in BA.2, N440K is at a contact residue site for sotrovimab. There are no acquired mutations associated with spike that are present in more than 1% of BA.2 sequenced samples. P169S is the only acquired NSP12 mutation occurring at over 1% prevalence in BA.2 and is not at a contact residue site associated with remdesivir or molnupiravir. No acquired mutations were observed in the NSP10 region of BA.2 and no mutations in NSP14 were observed occurring at over 1% prevalence.

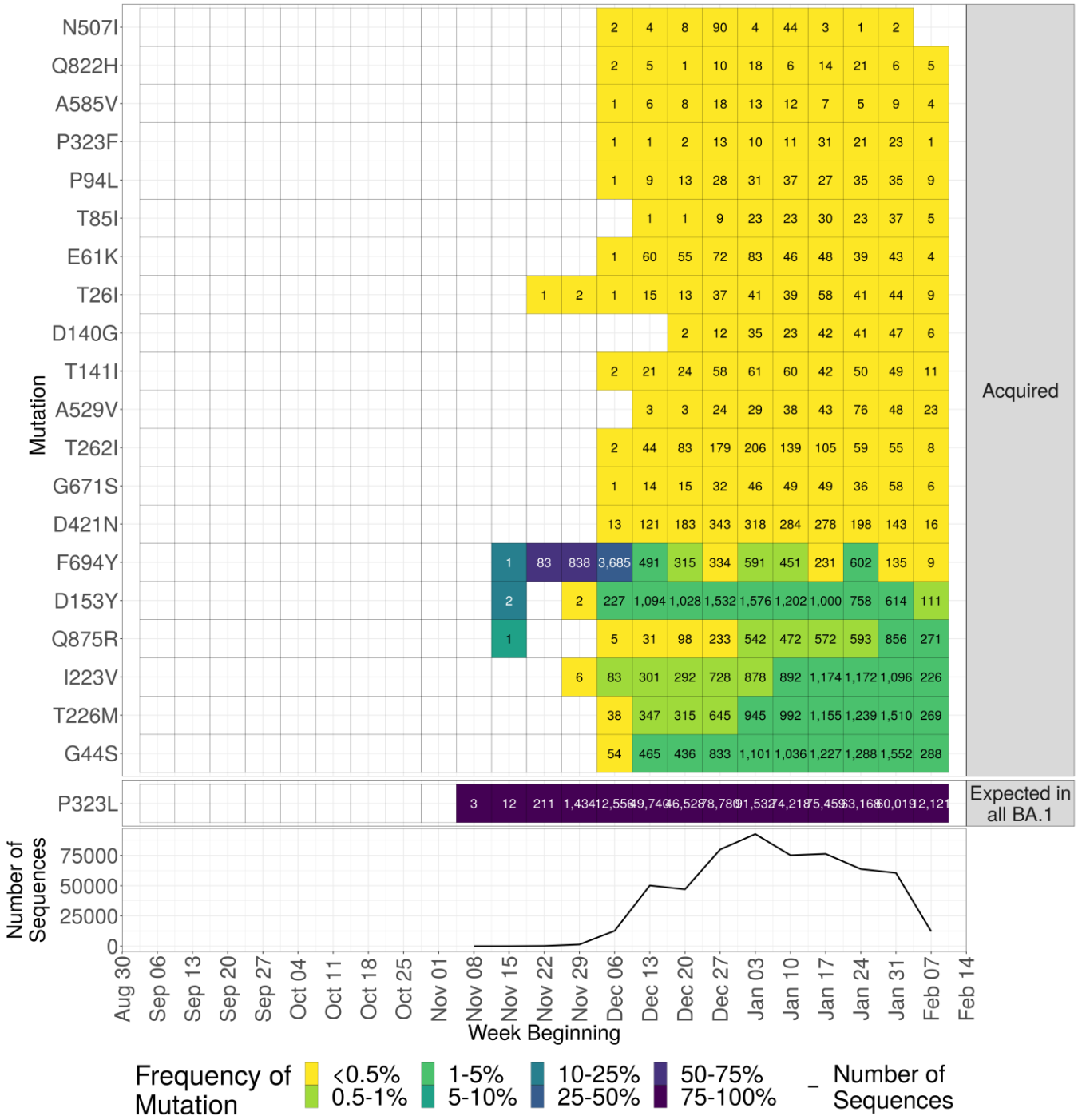
Figure 1 and Figure 2 show mutation heatmaps of non-synonymous changes accruing on top of the BA.1 lineage defining mutations. Figure 3 and Figure 4 show mutation heatmaps of non-synonymous changes accruing on top of the BA.2 lineage defining mutations. Casirivimab/imdevimab and sotrovimab are nMABs targeting the spike gene. NSP12 contains the predicted contact sites for remdesivir and molnupiravir. Each tile shows the proportion of sequences with each mutation per week. The total number of sequences is shown within the box. In NSP12, F694Y is reported to be an artifact in sequences using the Artic V4 primers as reported by Sanderson et al (2021).

Figure 1. Spike mutations found in BA.1 genomes in the UK dataset relative to the Wuhan sequence NC_045512.2



Supplementary data is not available. It should be noted all mutations in the sequence alignment are reported in these plots for review purposes. Those reported here at positions 145 and 211 arise due to base deletions affecting the sequence alignment and are not true, acquired mutations and are artifactual.

Figure 2. NSP12 mutations found in BA.1 genomes in the UK dataset relative to the Wuhan sequence NC_045512.2



Supplementary data is not available.

Figure 3. Spike mutations found in BA.2 genomes in the UK dataset relative to the Wuhan sequence NC_045512.2

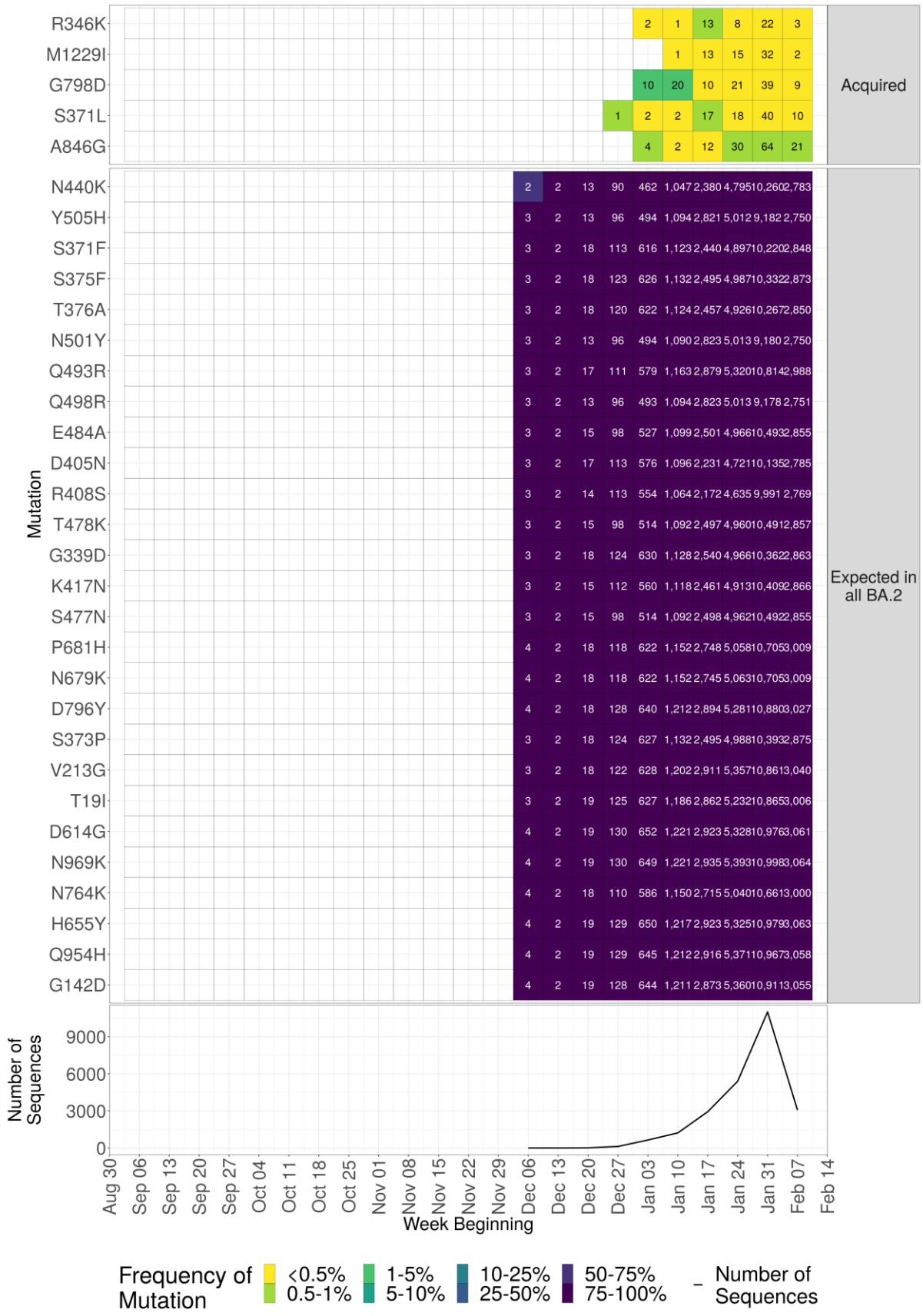
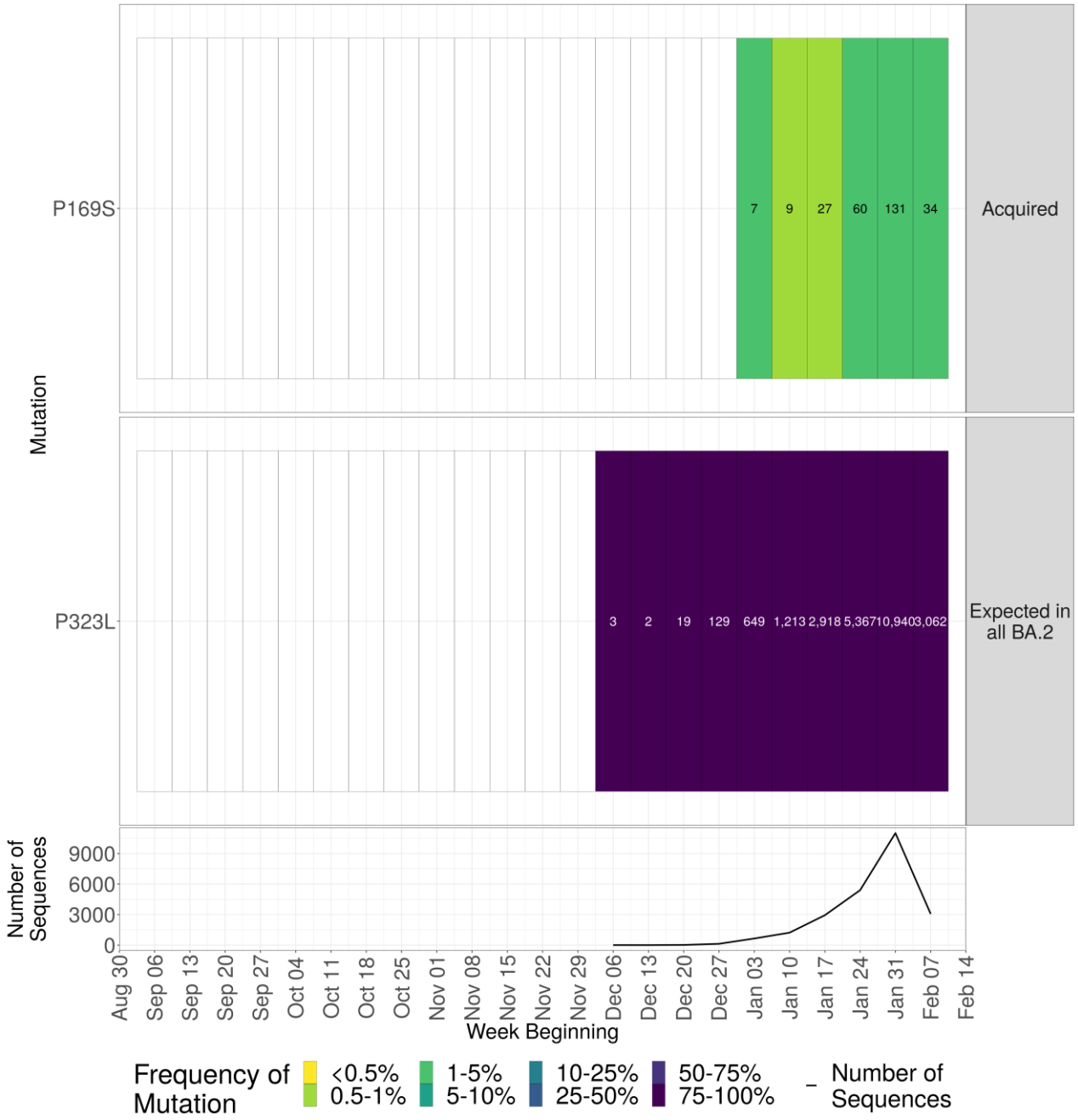


Figure 4: NSP12 mutations found in BA.2 genomes in the UK dataset relative to the Wuhan sequence NC_045512.2



Supplementary data is not available.

Post-treatment sequences

If a particular mutation is selected by treatment, it is expected to increase in frequency in viral genomes from treated patients. Residues in the spike, NSP10, NSP12 and NSP14 proteins that displayed distinct amino acid frequencies between pre- and post-treatment sequences were identified. These proteins were selected because they are theorised to interact with treatments currently in use (casirivimab/imdevimab, sotrovimab, molnupiravir and remdesivir). This analysis will be run weekly to scan for mutations which require further assessment.

Pre-treatment sequences are those obtained from patients with a sequenced sample within one week prior to treatment initiation (including the day of treatment initiation). All sequences sampled after treatment initiation were defined as post-treatment sequences. Table 1 shows the number of available full genome sequences pre- and post-treatment, for each treatment. Sequences were translated to amino acids for analysis. Analyses were split by SARS-CoV-2 variant (Delta and Omicron) and were conducted separately for each gene region (spike, NSP10, NSP12 and NSP14) and for each treatment. BA.1 and BA.2 were analysed together because there were less than 10 post-treatment BA.2 sequences; BA.1 and BA.2 post-treatment sequences will be stratified in future briefings. Note that sequence data were not available for a large number of patients who have undergone treatment, therefore conclusions may change.

Table 1: Number of pre- and post-treatment full genome sequences, broken down by treatment and by variant (Delta vs. Omicron)

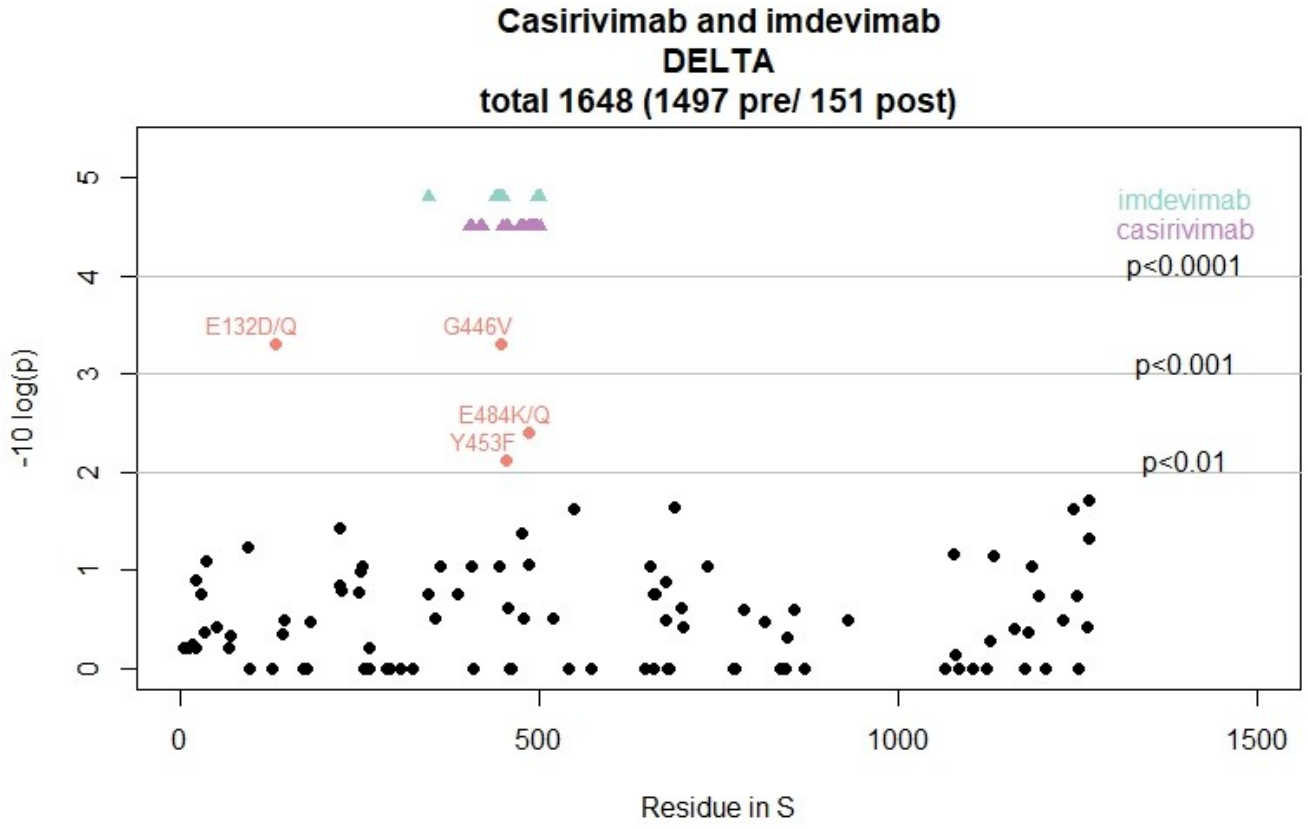
Treatment	Variant	Pre-treatment sequences	Post-treatment sequences
Casirivimab and imdevimab	Delta	1,497	160
Casirivimab and imdevimab	Omicron	86	56
Molnupiravir	Delta	24	6
Molnupiravir	Omicron	1,336	84
Remdesivir	Delta	3,470	596
Remdesivir	Omicron	544	217
Sotrovimab	Delta	27	3
Sotrovimab	Omicron	2,591	196

Note that counts reflect sequences rather than patients, a single patient may have more than one sequence and may be on more than one treatment and will be counted multiple times.

Six residues displayed diverging frequencies ($p<0.001$) between pre- and post-treated sequences, suggesting possible evidence of selection: E132D/Q and G446V in spike sequences from patients infected with the Delta variant and treated with casirivimab and imdevimab; N211S, P337L/R/S and E340A/D/K in spike in patients infected with the Omicron variant and treated with sotrovimab; and V394A in NSP14 in patients infected with Delta variant and treated with remdesivir (Figures 5, 6 and 7). For molnupiravir, no significant mutations were observed in the available data.

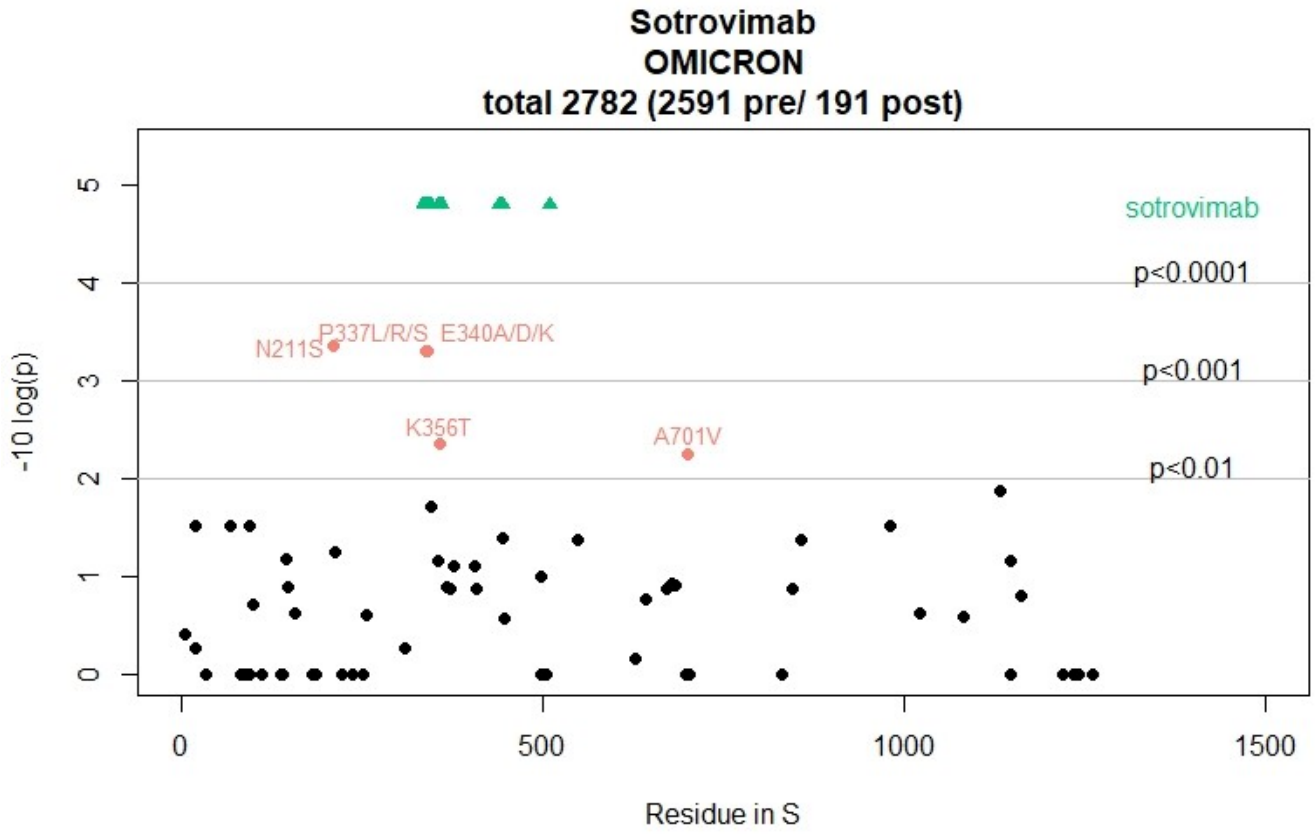
Further analyses of the mutations with increased frequency post-treatment will be undertaken, including in silico modelling and laboratory assessments.

Figure 5. P-values for differences in spike amino acid frequencies between pre- and post-casirivimab/imdevimab treatment sequences of patients infected with Delta



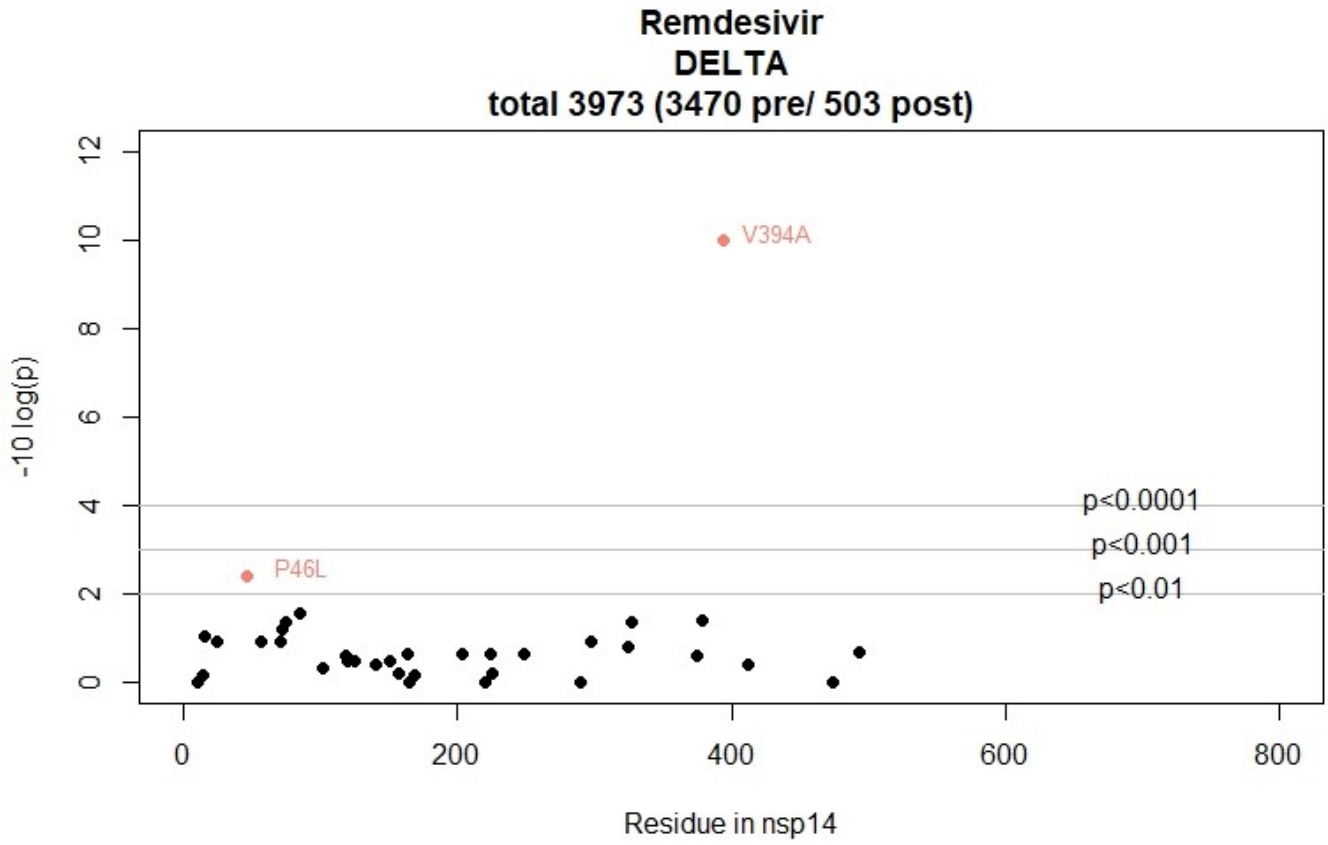
Amino acid frequencies were compared between pre- and post-treated samples at each site in the spike sequence alignment. P-values for each site were calculated using a Fisher's test, and p-values were log-transformed and inversed for visualisation so that sites with diverging values appear higher up on the figure. Only sites with some variability (>1 amino acid) are shown on the figure. The horizontal lines indicate p-value thresholds of p<0.01 and p<0.001. Residues with diverging frequencies (p<0.01) are highlighted in red, with the observed amino acid change indicated in text. Four sites displayed diverging frequencies at the 0.01 level between pre- and post-treatment sequence: E132D/Q, G446V, Y453F and E484K/Q. Residues 453 and 484 are known contact residues of casirivimab and residue 446 is a known contact residue for imdevimab. Given the large numbers of sites independently tested, lower p thresholds are necessary to demonstrate selection. Residues known to interact with each drug are indicated in blue and purple at the top of the figure. The numbers differ slightly from those in Table 1 because not all genomic data was sufficiently high quality for downstream sequence analysis. Supplementary data is not available.

Figure 6. P-values for differences in spike amino acid frequencies between pre- and post-Sotrovimab treatment sequences of patients infected with Omicron



Amino acid frequencies were compared between pre- and post-treated samples, for each site in the spike sequence alignment. P-values for each site were calculated using a Fisher's test, and p-values were log-transformed and inversed for visualisation so that sites with diverging values appear higher up on the figure. Only sites with some variability (>1 amino acid) are shown on the figure. The horizontal lines indicate p-value thresholds of p<0.01 and p<0.001. Residues with diverging frequencies (p<0.01) are highlighted in red, with the observed amino acid change indicated in text. Given the large numbers of sites independently tested, lower p thresholds are necessary to demonstrate selection. Five sites displayed diverging frequencies at the 0.01 level between pre- and post-treatment sequence: N211S, P337L/R/S, E340A/D/K, K356T and A701V. Residues 337, 340 and 356 are known contact residues for sotrovimab. The mutation S:N211S is an alignment artifact caused by a deletion at this position in Omicron. Currently there are only 3 BA.2 post-sotrovimab sequences, and these are included in the analysis. The numbers differ slightly from those in Table 1 because not all genomic data was sufficiently high quality for downstream sequence analysis. Supplementary data is not available.

Figure 7. P-values for differences in NSP14 amino acid frequencies between pre- and post-Remdesivir treatment sequences of patients infected with Delta



Amino acid frequencies were compared between pre- and post-treated patients, for each site in the NSP14 sequence alignment. P-values for each site were calculated using a Fisher's test, and p-values were log-transformed and inversed for visualisation so that sites with diverging values appear higher up on the figure. Only sites with some variability (>1 amino acid) are shown on the figure. The horizontal lines indicate p-value thresholds of $p<0.01$ and $p<0.001$. Residues with diverging frequencies ($p<0.01$) are highlighted in red, with the observed amino acid change indicated in text. Two sites displayed diverging frequencies at the 0.01 level between pre- and post-treated sequences: V394A ($p<0.00001$) and P46L ($p<0.01$). Given the large numbers of sites independently tested, lower p thresholds are necessary to demonstrate selection. The numbers differ slightly from those in Table 1 because not all genomic data was sufficiently high quality for downstream sequence analysis. Supplementary data is not available.

Sources and acknowledgments

Authors of this report

UKHSA COVID-19 Therapeutics Group
UKHSA Genomics Cell
UKHSA Outbreak Surveillance Team

Data and contributors

UKHSA Genomics Programme
NHS England and Improvement
University of Oxford

About the UK Health Security Agency

UKHSA is responsible for protecting every member of every community from the impact of infectious diseases, chemical, biological, radiological and nuclear incidents and other health threats. We provide intellectual, scientific and operational leadership at national and local level, as well as on the global stage, to make the nation's health secure.

UKHSA is an executive agency, sponsored by the Department of Health and Social Care.

Version 1.0

Published: March 2022
Publishing reference: GOV-11394