UK Health Security Agency

COVID-19 therapeutic agents: a programme of public health activities to support deployment of novel therapeutics for COVID-19

Therapeutics technical briefing 1

21 January 2022

Contents

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

1. Introduction

Therapeutics are a core public health mitigation measure for the next phase of the SARS-CoV-2 pandemic. The Department of Health and Social Care Therapeutics Task Force coordinates a pipeline of directly acting antiviral agents including monoclonal antibodies and small molecule drugs, for rapid deployment in the UK. Eligibility for therapeutic use for specific patient groups with coronavirus (COVID-19) is determined by NHS England and Improvement.

Casirivimab/imdevimab (Ronapreve®) has been in clinical use for inpatient use since 17 September 2021. Sotrovimab (Xevudy®) and molnupiravir have been in clinical use in community settings since 16 December 2021. Remdesivir received conditional marketing authorisation in the UK from the 24 December 2021.

There is a risk to therapeutics deployment both from the emergence of a dramatically altered variant such as Delta or Omicron, and from the more subtle emergence of mutations accruing in the existing prevalent variant, independently or as a result of the use of treatment.

The UK Health Security Agency's (UKHSA) programme of work aims to support rapid deployment of specific COVID-19 therapeutics by undertaking genomic, virological, and epidemiologic surveillance, through both national surveillance systems and academic collaboration. This report is produced to share information from these developing systems with partner organisations.

The programme will look to answer questions such as:

Is there any evidence that we are seeing mutations emerging which may cause resistance to deployed therapies?

Do such mutations form variants which are fit enough to spread in the community?

Is there any evidence that we are seeing changes in clinical outcomes which are suggestive of resistance or other causes of treatment failure?

Is there any evidence that there is inequity of access or use to COVID-19 treatments?

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. Analyses are experimental and findings will have a high level of uncertainty.

2. Programme of work

The UKHSA programme of work is outlined in Table 1.

Table 1. UKHSA programme of public health activities to support deployment of COVID-19 therapeutics

Workstream	Knowledge and evidence build	Structural modelling	Laboratory testing	Genomic surveillance	Epidemiology	Antimicrobial stewardship
Objective	Synthesise evidence on resistance risk and mechanisms	Provide structural modelling data on the likely impacts of variants and mutations	Provide laboratory data on the impacts of different variants and mutations	Monitor for emergence of mutations from workstream 1/2/3; analyse for mutations emerging de novo on treatment	Provide epidemiological surveillance on the use and outcomes of treatment (where appropriate given trials)	Support and monitor appropriate use of therapies to minimise the development of resistance
Partners	Agile Trial Panoramic Trial Recovery Trial	University of Oxford	Genotype to Phenotype Consortium		University of Edinburgh University of Oxford	NHS England and Improvement

Workstream 1. Knowledge and evidence build

This workstream aims to synthesise evidence on resistance risk by developing a living systematic review, incorporating published and grey data alongside real-time laboratory, genomic and epidemiology data from workstreams 2 to 5. Supplemented by clinical trial data from national clinical trials, this will be updated weekly and provide a comprehensive evidence base for the programme.

Workstream 2. Structural modelling

Protein model data is used to identify residues which may be associated with changed binding or activity of drugs. This feeds into the interpretation of genomic surveillance.

Workstream 3. Laboratory testing

UKHSA is assessing the activity of individual variants circulating in the UK against treatment agents by undertaking a standard panel of in vitro inhibitory investigations using Vero E6 cells for Victoria ('wild-type'), Beta, Delta, and Omicron isolates. Systems are in place to undertake in vivo testing for specific antivirals. New variants can be added to the workflow based on surveillance and or modelling data.

Workstream 4. Genomic surveillance

In addition to routine sequencing of a random sample of population positives in the community and hospital, a protocol has been introduced to enhance sequencing coverage of those who are receiving treatment (including initial and follow up sample). This protocol is currently being operationalised to cover community treated patients. Treated and untreated samples are analysed for evidence of emergent mutations.

Workstream 5. Epidemiological surveillance

Individual patient treatment data is being received from Blueteq[1] and can be linked to demographic, vaccination, hospital, outcome, and viral genomic data within UKHSA to provide epidemiological data on use and outcomes of individuals treated with novel therapeutic agents within England.

[1] Blueteq is a high-cost drug management system; doctors are required to complete a Blueteq form for any patient who is prescribed a high-cost drug.

Workstream 6. Antimicrobial stewardship

This workstream supports appropriate use of COVID-19 therapies by capturing and analysing clinical, epidemiological and prescription data to assess and improve stewardship of COVID-19 Therapeutics. This workstream also aims to monitor for prescription difficulties and challenges within stewardship practices as well as provide relevant education and training for infection teams leading on COVID-19 therapeutics. Daily dispensed data (provided by Rx-Info) will be used to assess the uptake of different key therapies by NHS acute Trusts and regionally in England and will be used to monitor equity of access to therapy.

3. Short summary of early data

3.1 Usage

The usage data for the therapeutics is summarised in Table 2.

Table 2. Usage of therapeutics in all settings as of (and including) 16 January 2022

	Patients with valid* treatment entries on Blueteq	Patients linked to daily COVID-19-line list	Patients with pre-treatment serology testing	Patients with at least one pre-treatment sequence	Patients with at least one post-treatment positive PCR	Patients with at least one post-treatment sequence**
Hospital						
Casirivimab/Imdevimab	4,962	4,811	3,135	2,051	1,270	270
Sotrovimab	457	450	275	64	109	4
Molnupiravir	-	-	-	-	-	-
Community						
Casirivimab/Imdevimab	82	79	6	6	11	3
Sotrovimab	3,370	3,291	890	634	339	20
Molnupiravir	3,659	3,557	134	669	433	35
All settings						
Remdesivir	46,966	43,988	3,263	9,387	Data not available	2,342

*Valid treatment entries include all treatment requests with a valid NHS number that have been approved, and do not include duplicate or future dated requests.
**Some samples are being analysed and some may be unsequenceable as they represent late infection.
Patients linked to daily COVID-19 line list = number of patients linked to the COVID-19 daily line list, mortality data and NIMS data.
Patients with pre-treatment serology testing = patient has had a pre-treatment antibody test recorded for SARS-CoV-2.
Patients with at least one pre-treatment sequence = patient has had at least one pre-treatment sequence.
Patients with at least one post-treatment positive PCR = patient has had at least one positive test for SARS-CoV-2 post-treatment and would be eligible for post-treatment sequencing.
Patients with at least one post-treatment sequence = patients with at least one sequence in the genomics line list after treatment.

An overview of the national dispensed data for the therapeutics is summarised in Table 3. Dispensed drug data will be used for analysis on equitable access to therapy and stewardship.

Table 3. Dispensed data for therapeutics as of (and including) 16 January 2022

Therapeutics		Reporting duration	Dispensed quantity
Ronapreve (Casirivimab/ Imdevimab) [co-packaged vials]	Casirivimab 300mg plus imdevimab 300mg	1 Oct 2021 to 16 Jan 2022	20,503
	Casirivimab 1332mg plus imdevimab 1332mg	7 Dec 2021 to 16 Jan 2022	897
Sotrovimab [single 500mg/8ml vials]		20 Dec 2021 to 16 Jan 2022	5,609
Molnupiravir [packs of 40x200mg capsules]		6 Dec 2021 to 16 Jan 2022	5,426

3.2 Genomic surveillance

Omicron BA.1 is now the UK's predominant variant (see Variant Technical Briefing 34). There are a small but increasing number of BA.2 cases.

Genomic surveillance analysis utilises information on residues which are involved in drug binding, based on modelling studies. Residues of interest were identified by selecting structural models of SARS CoV-2 proteins of interest in complex with either therapeutic antibodies or small molecule inhibitors, which have been deposited in the protein data bank (A Structural View of Biology). These structural models were analysed visually by the modelling team using molecular graphics programs and by using the software at European Bioinformatics Institute, Proteins, Interfaces, Structures and Assemblies (EBI PISA) for the analysis of interfaces between protein-antibody or protein-inhibitor complexes. SARS-CoV-2 amino acid residues at the interface forming hydrogen bond contacts or hydrophobic interactions were identified and compiled into lists for sequence analysis.

Figure 1 and Figure 2 show mutation heatmaps of non-synonymous changes accruing on top of the Omicron lineage defining mutations in Omicron lineage BA.1. Casirivimab/imdevimab and sotrovimab are monoclonal antibodies 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 and others (2021).

The treatments used now that Omicron is predominant are sotrovimab, molnupiravir and remdesivir. Of the lineage defining Spike mutations in Omicron, N440K is at a contact residue

site for sotrovimab. The additional Spike mutations occurring at over 1% prevalence in BA.1 in the last week are N211S, R346K, L452R, A701V, and I1081V. Of these, R346K is at a predicted contact residue site for sotrovimab. There are no mutations observed in NSP12 at contact residue sites associated with remdesivir or molnupiravir.

Figure 1. Spike mutations found in Omicron genomes in the UK dataset relative to the Wuhan sequence NC_045512.2
Supplementary data is not available

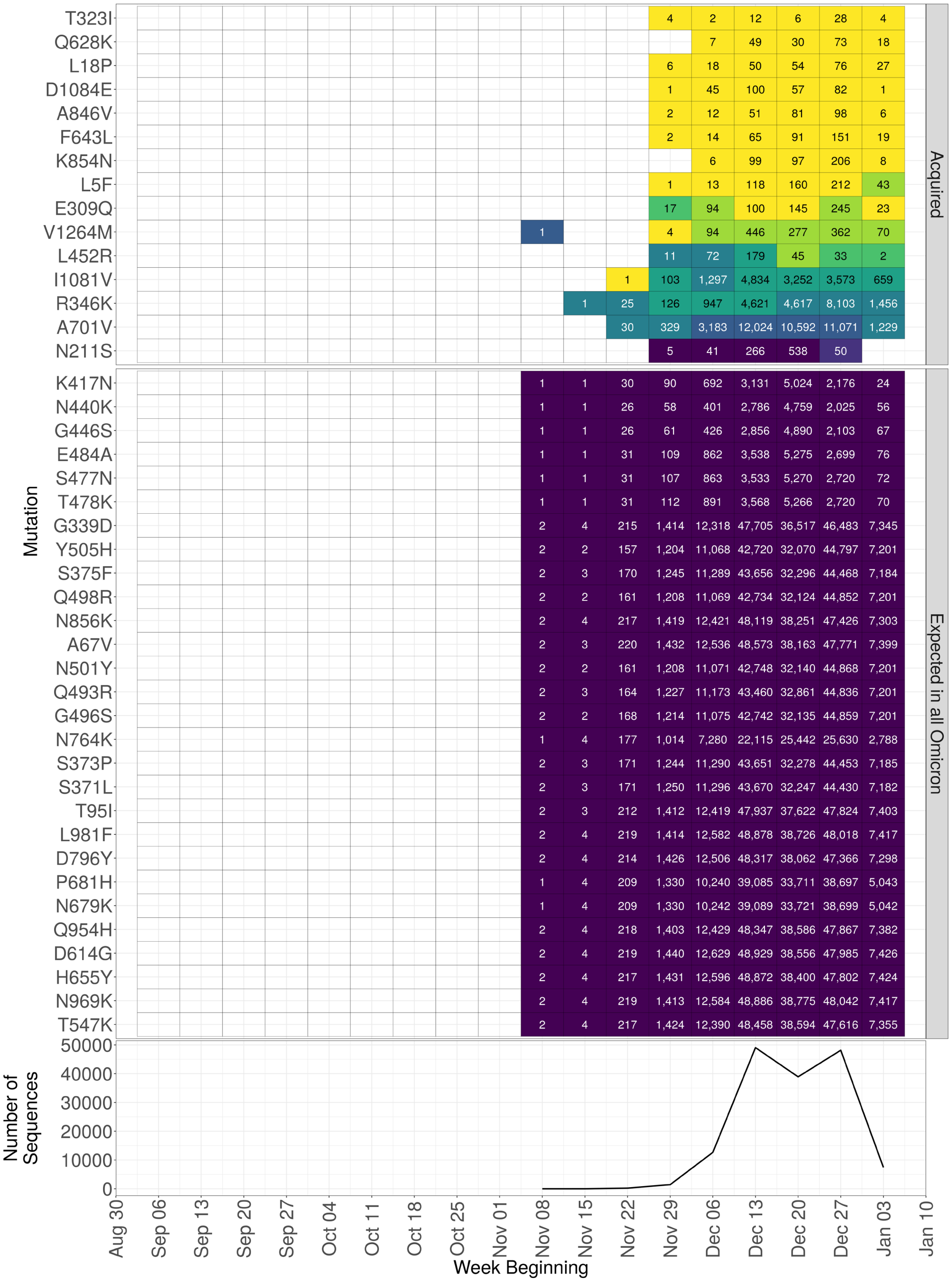
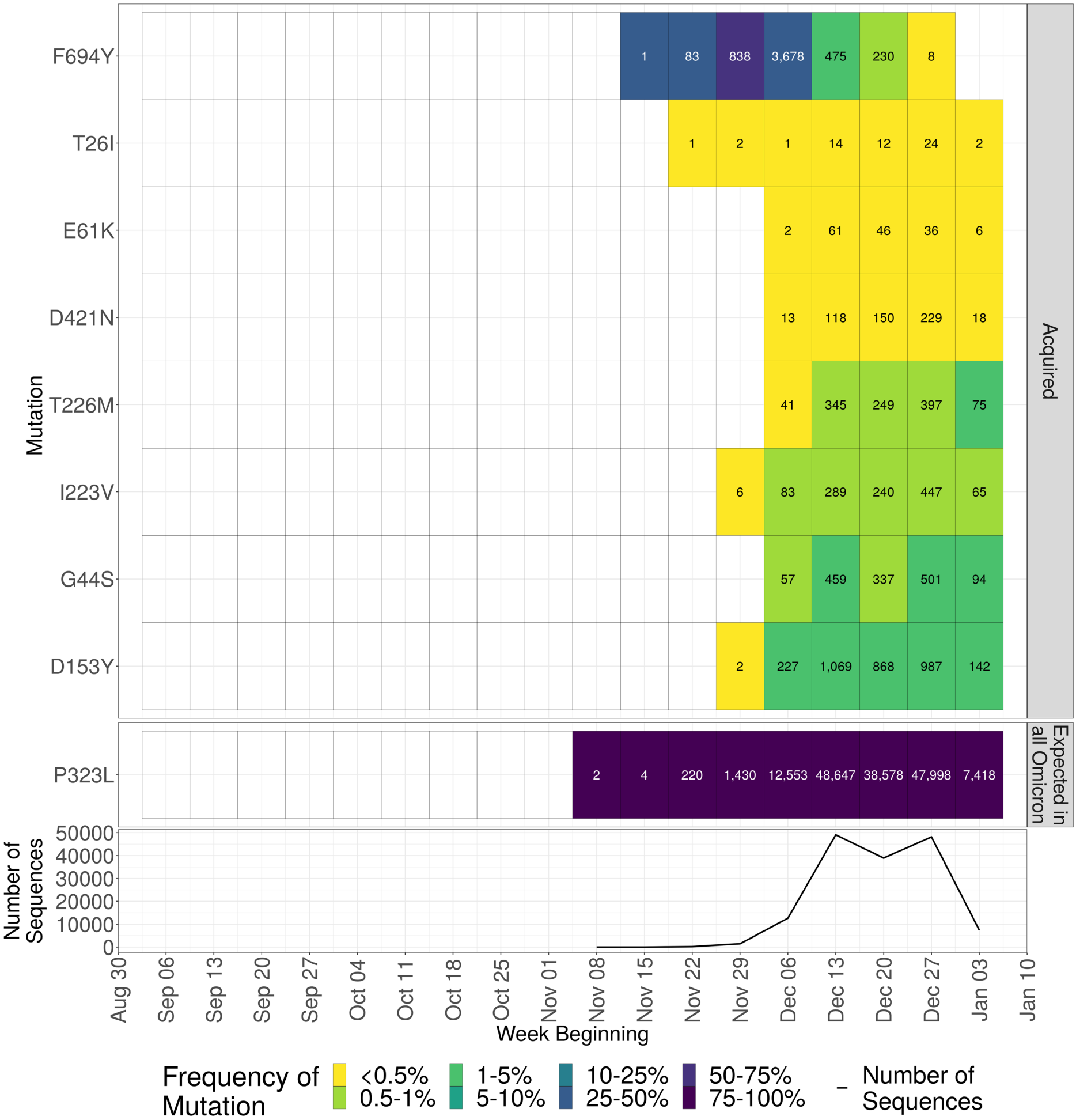


Figure 2. NSP12 mutations found in Omicron genomes in the UK dataset relative to the Wuhan Sequence NC_045512.2
Supplementary data is not available



Post-treatment sequences

If a particular mutation is selected for treatment, it is expected to increase in frequency in viral genomes from treated patients. Residues in Spike protein that displayed distinct amino acid frequencies between pre- and post-treatment sequences were identified. This analysis will be run weekly to scan for mutations which require further assessment.

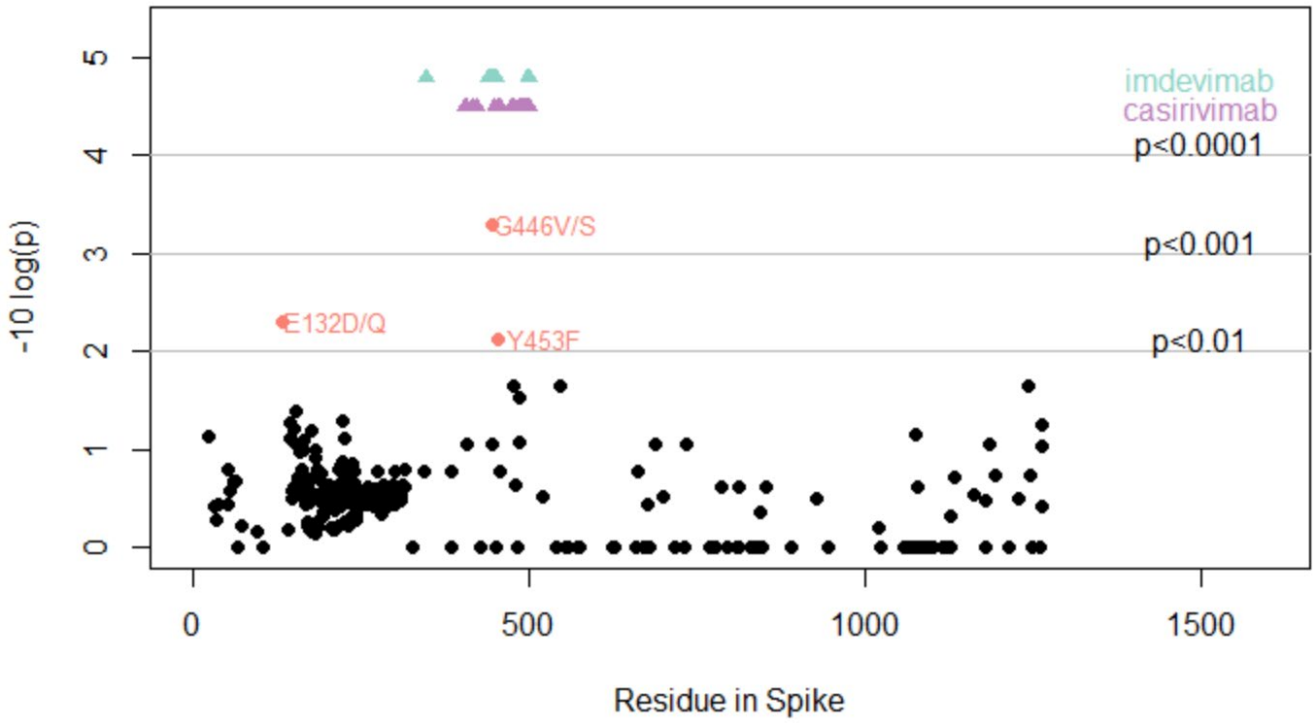
Pre- and post-treatment sequences were sampled. Pre-treatment sequences were obtained from all patients who went on treatment and who had a pre-treatment sequence within one week prior to treatment initiation (including the day of treatment initiation). At present there are sufficient sequences only for analysis of post-casirivimab/imdevimab sequences in Delta infected patients. This analysis will be expanded to other treatments once further data becomes available.

Currently one residue (G446) known to interact with imdevimab is suggestive of selection. A valine amino acid was observed in 6 out of 104 (5.8%) treated sequences for whom the amino acid could be determined at this position, compared to only 1 out of 1,130 (0.09%) untreated sequences (Figure 3 below). Post-treatment sequences with G446V were confirmed to originate from 6 different patients. However, only 5 patients have pre- and post-treatment sequences indicating a change from a G to a V (Figure 3 below). This position will be monitored through the weekly analysis.

As indicated in Figure 3, G446V is present in <0.5% of Delta and AY.4.2 sequences.

Figure 3. P-values for differences in amino acid frequencies between pre- and post-casirivimab/imdevimab treatment sequences

P-values were calculated using a Fisher's test. Only residues with some variability (>1 amino acid) are shown. The horizontal lines indicate p-value thresholds of p<0.01 and p<0.001 (although given the large numbers of sites independently tested, lower p thresholds should be employed). Residues known to interact with each treatment utilised are indicated in blue and purple at the top of the figure. Residues with diverging frequencies (p<0.01) are highlighted in red, with the observed amino acid change indicated in text.



Drug resistance risk assessment

The therapeutic agent risk assessment is in development.

Sources and acknowledgments

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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.

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