UK Health Security Agency

SARS-CoV-2 variants of concern and variants under investigation in England

Technical briefing 45

9 September 2022

This report provides an update on previous briefings up to 22 July 2022

Contents

Summary

This report has been published to share the detailed variant surveillance analyses which contribute to the variant risk assessments and designation of new SARS-CoV-2 variants. This specialist technical briefing contains early data and analysis on emerging variants and findings have a high level of uncertainty.

Unless stated otherwise, this technical briefing uses a data cut-off of 5 September 2022 to allow time for analyses.

Interpreting variant data

The current testing policy needs to be considered when interpreting all variant data; the targeting of testing at specific groups is likely to delay the detection and characterisation of variants.

BA.5

BA.5 is the predominant circulating variant in the United Kingdom (UK).

BA.4/BA.5 Severity

Analysis of the relative risk of admission to hospital as an inpatient following presentation to emergency care, comparing BA.4 and BA.5 to BA.2 found no evidence for a difference in risk between the variants.

Newly designated variant – V-22SEP-01 (BA.4.6)

Omicron sub-lineage BA.4.6 was identified as part of horizon scanning on 15 August 2022. On 1 September 2022 BA.4.6 was designated as variant V-22SEP-01.

BA.4.6 has a mutation in a known antigenically significant site (S: R346T) and an apparent small growth advantage relative to BA.5. BA.4.6 represented 3.31% of UK samples for the week beginning 14 August 2022.

The University of Oxford reported preliminary neutralisation data to the Variant Technical Group. Pseudoviral neutralisation assays performed on BA.4.6 show that titres are reduced 2-fold, compared to neutralisation of BA.4 or BA.5 using sera from triple dosed recipients of the Pfizer BNT162b2 vaccine.

V-22JUL-01 (BA.2.75)

As of 6 September 2022, there were 89 cases with BA.2.75 in England. BA.2.75 is currently increasing in frequency in England. The growth rate increased from July 2022 to August 2022 and is currently 61% per week compared to co-circulating lineages.

Two sub-lineages of BA.2.75 (BA.2.75.1 and BA.2.75.2) are currently being assessed. Sub-lineage BA.2.75.1 is defined by the addition of S:D574V, and sub-lineage BA.2.75.2 by the addition of S:R346T, S:F486S, S:D1199N. Sub-lineage BA.2.75.2 was first identified as part of horizon scanning on 20 August 2022 and was made a signal in monitoring on 7 September 2022.

Published information on variants

On 1 April 2022 UK Health Security Agency (UKHSA) amended its variant classification system. Further details are available in Technical Briefing 39.

SARS-CoV-2 Routine variant data update covers surveillance data and sequencing coverage data on all other variants of concern (VOCs) and variants under investigation (VUIs) up to 25 March 2022.

The collection page gives content on variants, including prior technical briefings. Technical briefings are published periodically. From Technical Briefing 15, briefings include variant diagnoses identified by whole-genome sequencing and a genotyping polymerase chain reaction (PCR) test, including the categorisation of sequenced and genotyped variant results and a rules-based decision algorithm to identify variant and mutation profiles from genotype assay mutation profiles.

The Public Health England repository from 5 March 2021 contains the previous genomic definitions for VOCs and VUIs.

Part 1. Surveillance overview

World Health Organization (WHO) nomenclature from 24 January 2022 is incorporated. Tables 1a and 1b show the current VOCs, variants (V-date-number), and signals in monitoring detected and not detected in the UK incorporating WHO designations with Phylogenetic Assignment of Named Global Outbreak Lineages (Pangolin lineages).

Table 1a. Variants detected in the UK in the past 12 weeks

Variants of concern	Variants (Vs)	Signals in monitoring
Omicron (B.1.1.529) sub-lineage BA.1 and descendant lineages VOC-21NOV-01	V-22MAY-01 (BA.2.12.1)	BA.3
Omicron (B.1.1.529) sub-lineage BA.2 and descendant lineages VOC-22JAN-01	Delta (B.1.617.2 and sub-lineages) V-21APR-02	Delta and Omicron recombinant lineages (UK)
Omicron (B.1.1.529) sub-lineage BA.4 VOC-22APR-03	XE Recombinant (BA.1 x BA.2) V-22APR-02	BA.4.7
Omicron (B.1.1.529) sub-lineage BA.5 VOC-22APR-04	V-22JUL-01 (BA.2.75)	BA.2.75.2
	V-22SEP-01 (BA.4.6)	

Table 1b. Variants detected in GISAID, but not in the UK, in the past 12 weeks

Variants of concern	Variants (Vs)	Signals in monitoring
	Alpha (V-20DEC-01/B.1.1.7)	XAW (BA.2 x Delta recombinant)
	B.1.617.3 V-21APR-03	BA.2.3.20
	V-21OCT-01 (AY.4.2)†	

† AY.4.2 is a sub-lineage within Delta that has been assigned as a distinct V-date-number

VOCs and other variants (V-date-number) are monitored weekly for observations within the last 12 weeks. If variants have not been detected in the UK within this period, they are

moved to international status with continued monitoring. If a VOC or variant has not been observed in the UK or international data sets within the preceding 12 weeks, it is designated as provisionally extinct, but monitoring remains in place. Variants and signals in monitoring may also be removed from the grid if they show consistently low growth rates.

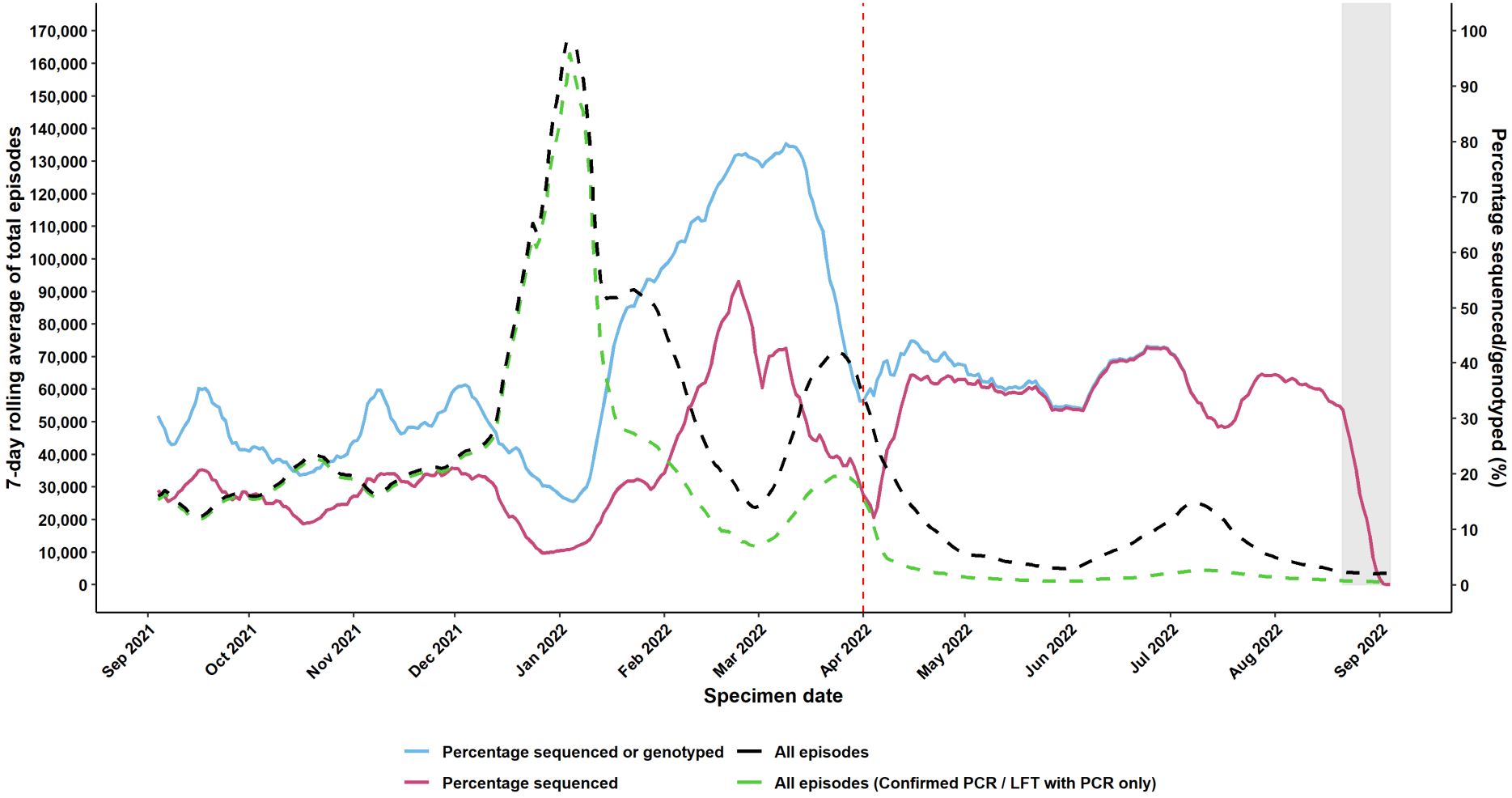
1.1 Sequencing coverage

Figure 1 shows the proportion of coronavirus (COVID-19) episodes as detected by PCR that have linked to a valid sequencing result (sequences included have 50% of the genome with sufficient read coverage) or genotyping PCR result over time. Figure 2 shows the proportion of episodes sequenced and genotyped over time by regions. Figure 3 shows the proportion of episodes sequenced and genotyped amongst individuals who tested positive whilst in hospital. The vertical dashed red line indicates the 1 April 2022 when free testing for the general public ended.

Sequencing coverage of PCR confirmed episodes were high during March 2022 (Figure 1) However, this needs to be interpreted with care as PCR tests have declined substantially since mid-February 2022 and case ascertainment is reduced.

Currently, the sequencing strategy prioritises hospitalised cases, patients who are receiving specific antiviral therapy, and national core priority studies.

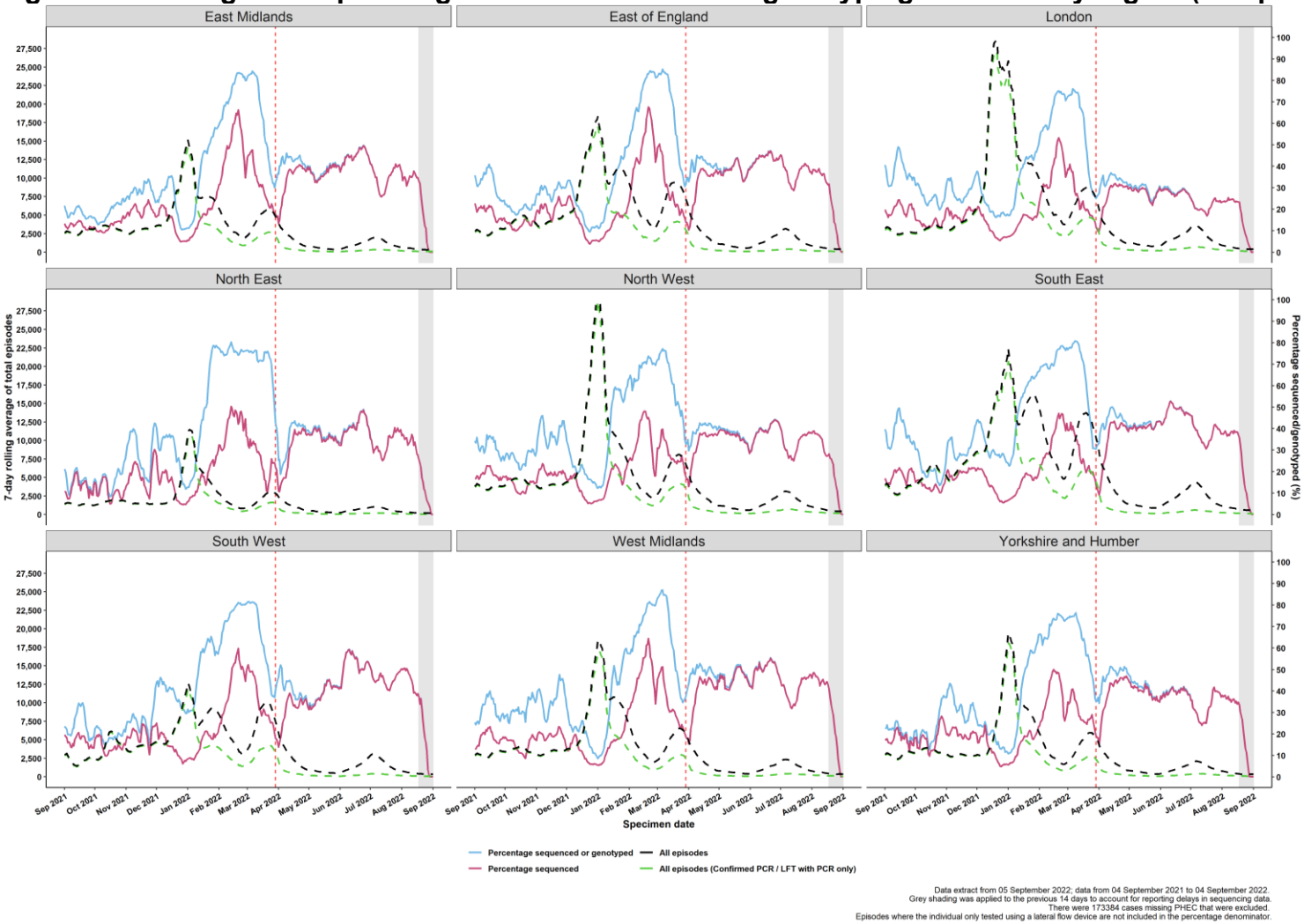
Figure 1. Coverage of sequencing with a valid result and genotyping over time (4 September 2021 to 4 September 2022)



Data extract from 05 September 2022; data from 04 September 2021 to 04 September 2022.
Grey shading was applied to the previous 14 days to account for reporting delays in sequencing data.
Episodes where the individual only tested using a lateral flow device are not included in the percentage denominator.

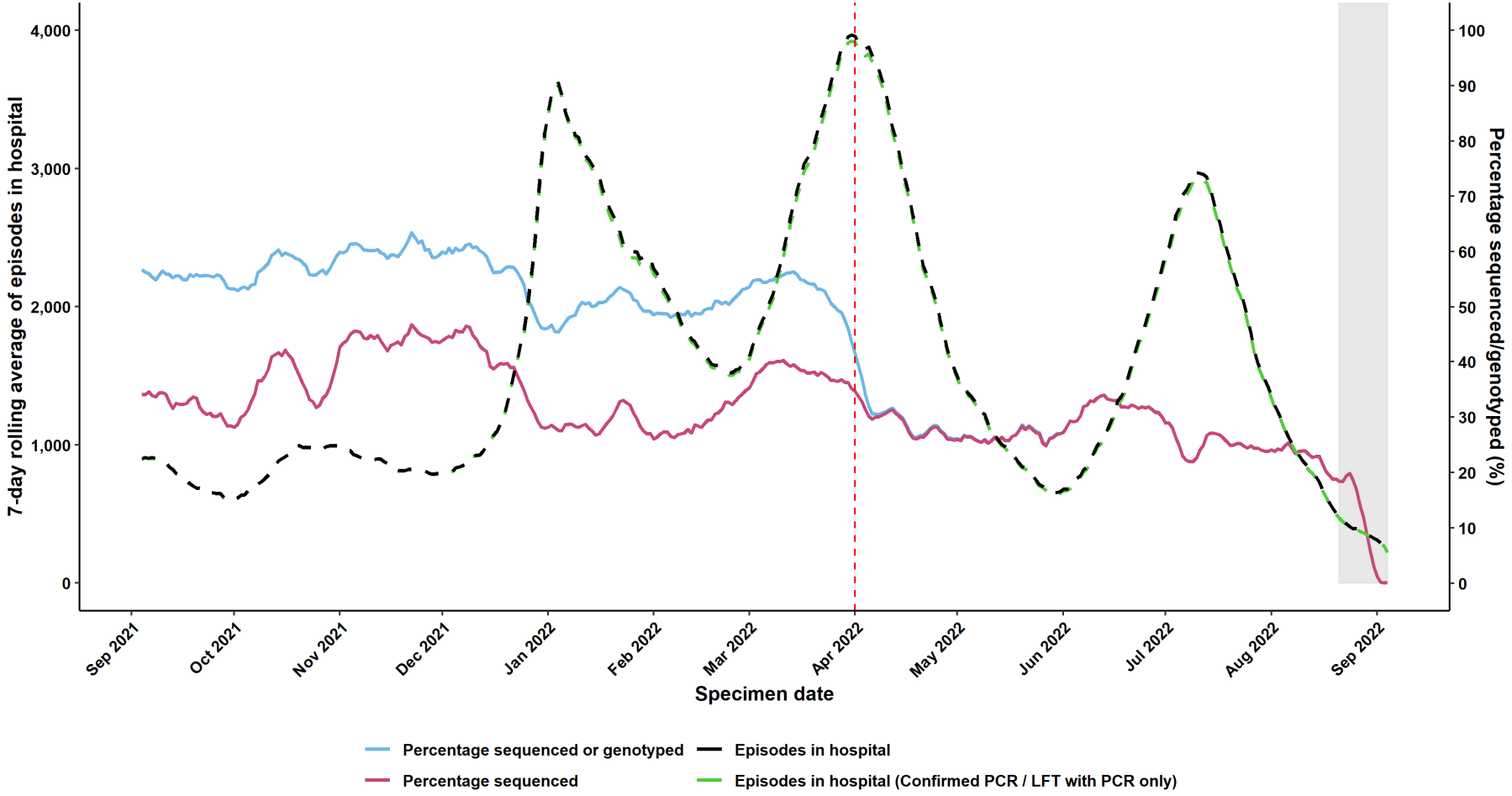
Episodes where the individual only tested using a lateral flow device are excluded. Grey shading was applied to the previous 14 days to account for reporting delays in sequencing data. (The data used in this graph can be found in the accompanying spreadsheet.)

Figure 2. Coverage of sequencing with a valid result and genotyping over time by region (4 September 2021 to 4 September 2022)



Episodes where the individual only tested positive using a lateral flow device are excluded. Grey shading was applied to the previous 14 days to account for reporting delays in sequencing data. (The data used in this graph can be found in the accompanying spreadsheet.)

Figure 3. Coverage of sequencing with valid result and genotyping for cases who test positive in hospital (4 September 2021 to 4 September 2022)



Data extract from 05 September 2022; data from 04 September 2021 to 04 September 2022.
Grey shading was applied to the previous 14 days to account for reporting delays in sequencing data.
Episodes where the individual only tested using a lateral flow device are not included in the percentage denominator.

Episodes where the individual only tested positive using a lateral flow device are excluded. Grey shading was applied to the previous 14 days to account for reporting delays in sequencing data. (The data used in this graph can be found in the accompanying spreadsheet.)

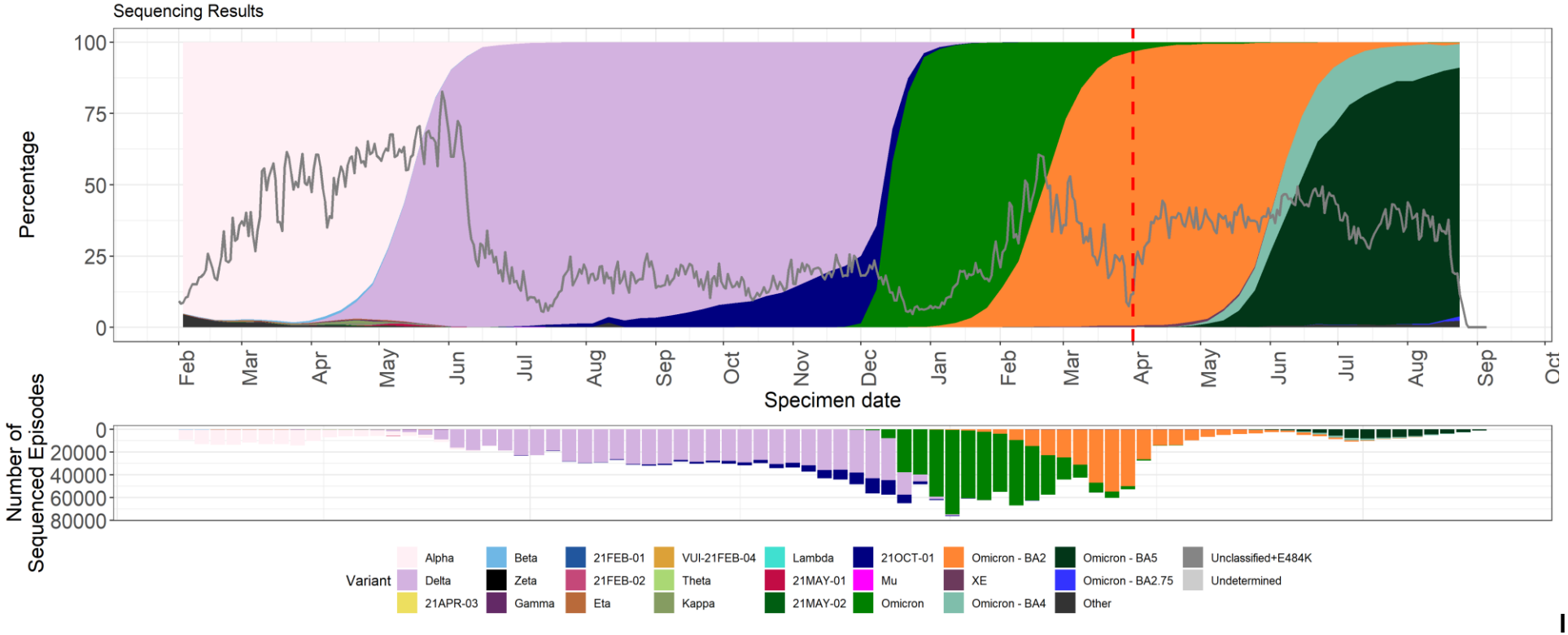
1.2 Variant prevalence

The prevalence of different UKHSA-designated variants amongst sequenced episodes is presented in Figure 4 . Of the sequenced episodes from 21 August 2022 to 28 August 2022, 0.5% were BA.2 (VOC-22JAN-01), 8.3% BA.4 (including BA.4.6, that is, lineages captured by VOC-22APR-03), 87.2% BA.5 (VOC-22APR-04), 1.6% BA.2.75 (V-22JUL-01) and 2.4% were classified as other.

The prevalence of variants amongst sequenced episodes by Pangolin designation is presented in Figure 5. Lineages are shown if there are more than or equal to 5,000 sequences since 3 January 2022 or if they are more than or equal to 1% of sequences within a single week over the last 6 weeks. Lineages that do not meet these criteria are combined with their parent lineage (for example, BA.2.4 is combine with BA.2).

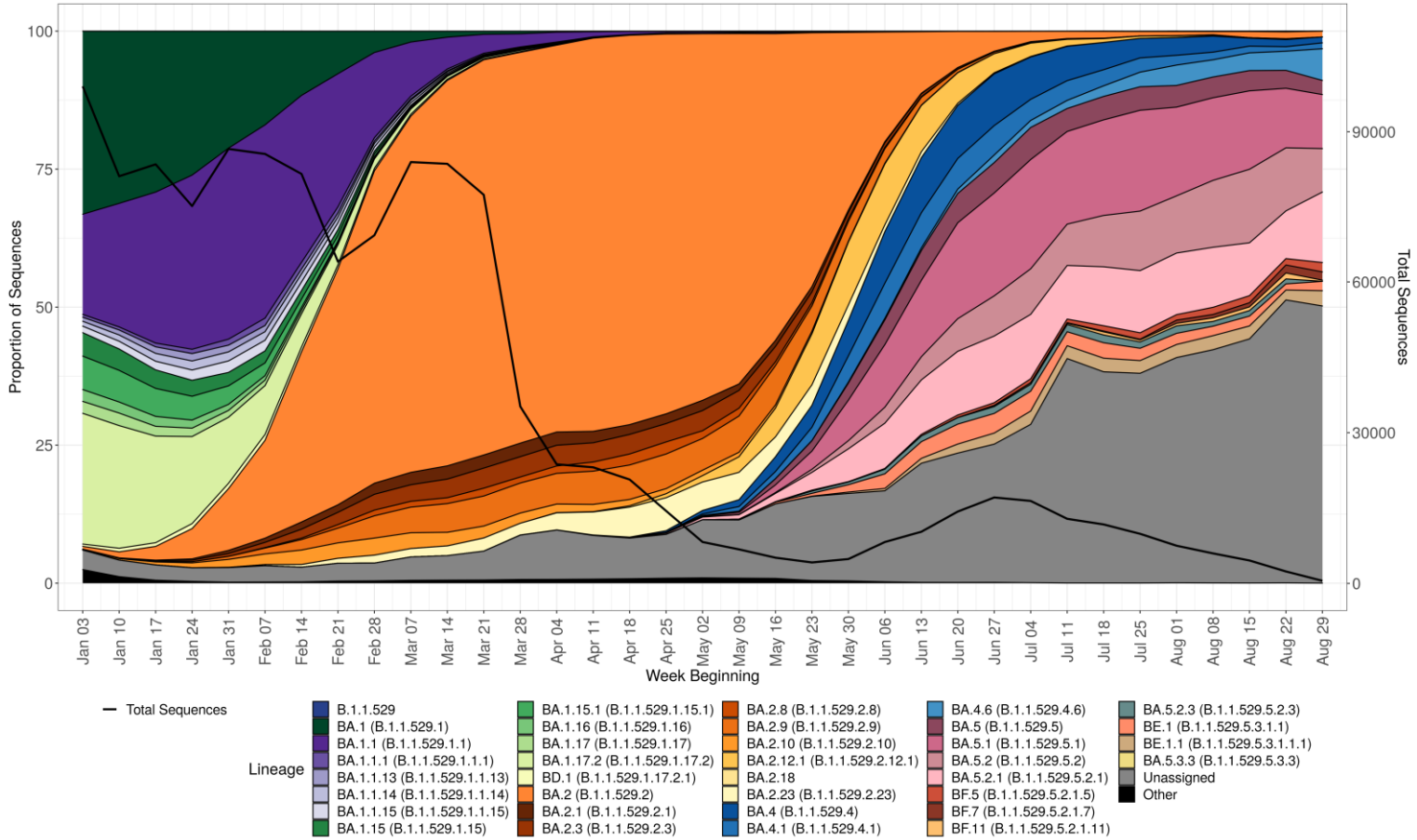
Due to the increasing similarities across BA sub-lineages, it is difficult to assign lineages to sequences with lower genome coverage. Therefore, an increasing proportion of sequences are classed as unassigned by Pangolin although they can still be identified at the level of the UKHSA definition (Figure 5). Of the 12,725 sequences that are unassigned by Pangolin since 25 July 2022, UKHSA variant classifications define 11,352 (89.21%) as VOC-22APR-04, 773 (6.07%) VOC-22APR-03, 98 (0.77%) VOC-22JAN-01, 20 (0.16%) V-22JUL-01,1 (0.01%) VOC-21NOV-01, and 192 (1.51%) as an undetermined Omicron lineage and they will be reported as such in UKHSA outputs. The remainder are low quality genomes and have not been assigned to a UKHSA variant.

Figure 4. Variant prevalence of available sequenced episodes for England from 1 February 2021 as of 6 September 2022



Find accessible data used in this graph in underlying data. Dashed lines indicate period incorporating issue at a sequencing site. Grey line indicates proportion of cases sequenced. The red dash line denotes the start of England's 'Living with COVID' Plan. Note recombinants, such as XD, are not specified but are largely within the 'other' group currently as numbers are too small.

Figure 5. Prevalence of Pangolin lineages in the UK with sequence data from 3 January 2022 to 4 September 2022



The total number of valid sequence results per week is shown by the black line. The “Other” category in this plot contains all lineages that do not meet the relevant criteria after combining smaller sub-lineages. “Unassigned" are sequences that could not be assigned a lineage by Pangolin. Find accessible data used in this graph in underlying data.

1.3 Variant modelling

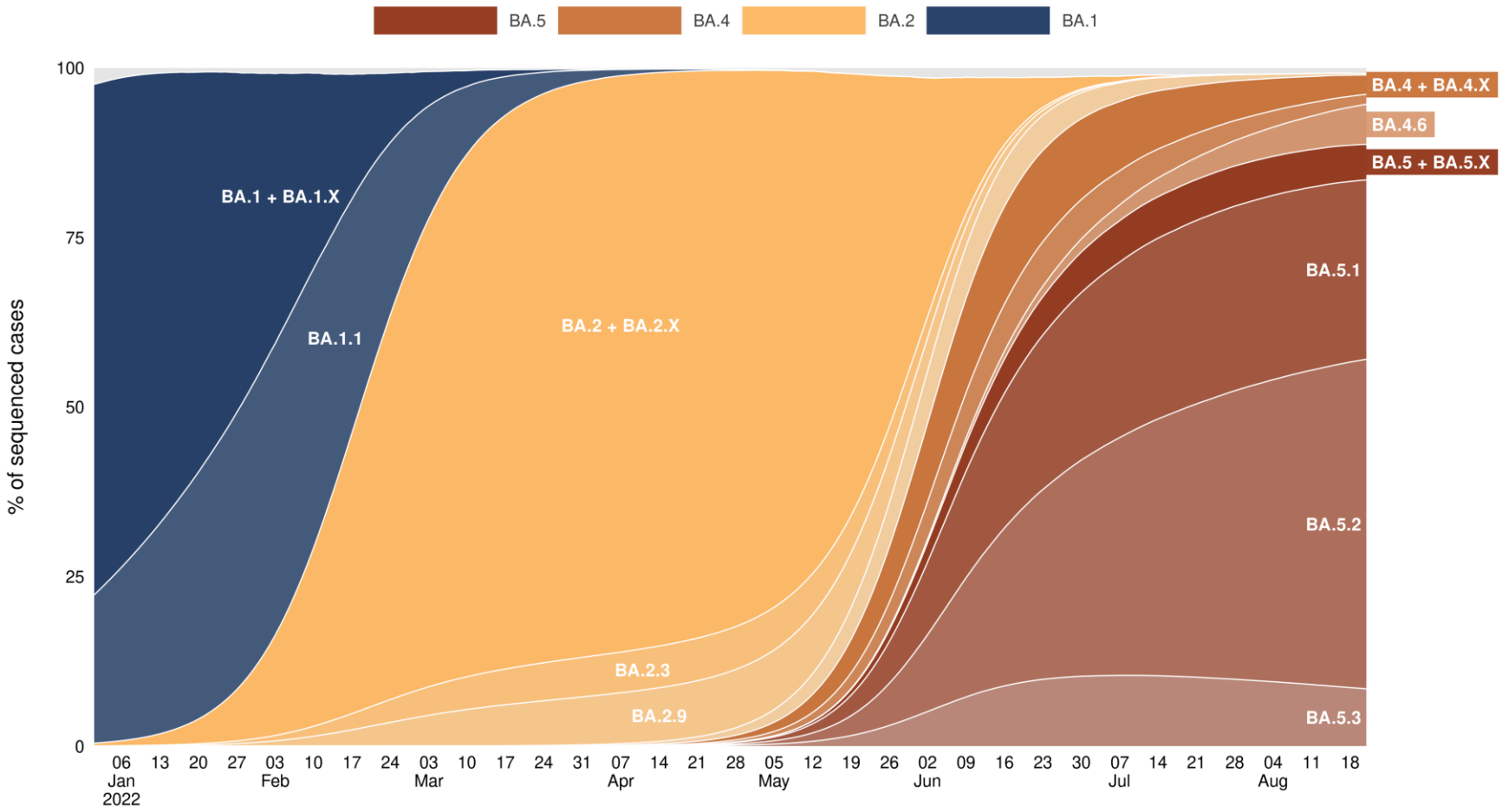
Multinomial model

A Bayesian multinomial model was used to describe the dynamics of Omicron lineages in England between 1 January 2022 and 21 August 2022, to model the relative fitness advantages of Omicron lineages. The model accounts for regional heterogeneity in lineage arrival times.

The data is sourced from the Sanger Mart, where the version of Pangolin used to classify lineages will differ to the in-house UKHSA definitions outlined above. Some lineage classes are combinations of several lineages; any sub-lineage with a small number of samples is folded in with its parent lineage (for example, BA.2 + BA.2.X includes all BA.2 lineages not explicitly modelled). A small percentage (less than 5%) of samples that could not be assigned a probable parent lineage. It should be noted that this model uses Pangolin calls that are subject to change and are not as robust as the UKHSA variant calls from elsewhere in this report.

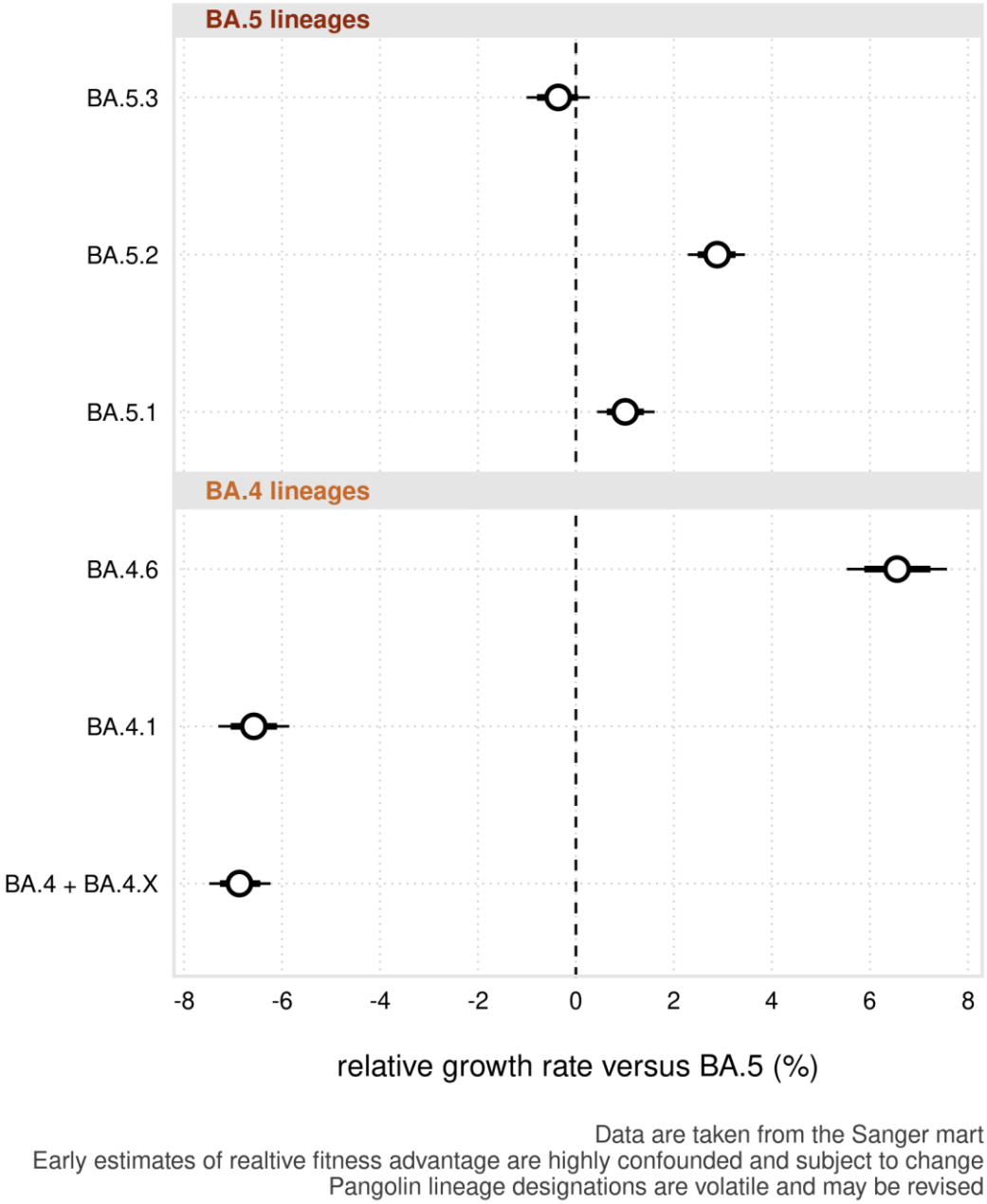
The modelled percentage representation is shown in Figure 6 and the estimated relative growth rates for each Omicron lineage is given in Figure 7. BA.5 is the dominant parent lineage in the UK, with BA.2 lineages having the larger fitness advantage. Early estimates of the relative fitness advantage of BA.4.6 suggest that it has a 6.55% (95% credible interval (CrI) 5.53 to 7.57) advantage over BA.5 (Figure 7). This is considerably smaller than the advantage of BA.5 over BA.2, which had a 45 to 55% relative fitness advantage.

Figure 6. Area plot showing the predicted representation of each lineage of the multinomial model



This figure shows the predicted representation of different lineages from the multinomial model. The grey region denotes other non-Omicron or recombinant lineages. Supplementary data is not available for this figure.

Figure 7. Comparison of the estimated relative growth rates for BA.5 and BA.4 lineages versus that for specifically BA.5 and other low count BA.5 lineages (BA.5 + BA.5.X)



The relative growth rates are taken from a multinomial model of sequenced Pillar 2 cases in England, described above. Supplementary data is not available for this figure.

Table 2. Modelled percentage for the national representation of emerging BA.2, BA.4 and BA.5 lineages from the multinomial model. Estimates are for 21 August 2022

Lineage	Median %	Upper CrI	Upper CrI	Parent lineage total
BA.5.2	48.6	36.53	60.74	88.72
BA.5.1	26.43	17.29	36.69	88.72
BA.5.3	8.44	5.22	13.01	88.72
BA.4.6	5.91	3.68	9.39	10.22
BA.5 + BA.5.X	5.25	3.32	8.09	88.72
BA.4 + BA.4.X	2.84	1.74	4.57	10.22
BA.4.1	1.47	0.93	2.42	10.22
BA.2.12.1	0.24	0.15	0.39	0.24
BA.5.2	48.6	36.53	60.74	88.72
BA.5.1	26.43	17.29	36.69	88.72
BA.5.3	8.44	5.22	13.01	88.72

Relative growth rates

The representation of different lineages among sequenced Pillar 2 cases was modelled for the last 3 months in England. After the testing policy change on 1 April 2022 the composition of Pillar 2 tests is less well defined. We exclude tests associated with travellers, but these data are still likely confounded by targeted testing. These limitations may bias estimates of relative growth. Generalised additive models are fit with a negative binomial error structure to counts of lineages to determine growth rates. An offset term is used to control for sampling effort.

We fit models both the weekly timescale by lineage (due sample sizes) and on the daily timescale by coarser definitions (BA.5, BA.4 and BA.4.6, see Table 3). For the weekly timescale, only variants that were sequenced 10 or more times in the past 2 weeks are included (Figure 8). Estimates in Figure 8 are for the week ending 4 September 2022. This data is sourced from the Sanger Mart, where the version of the version of Pangolin used to classify lineages will differ to the in-house UKHSA definitions outlined above.

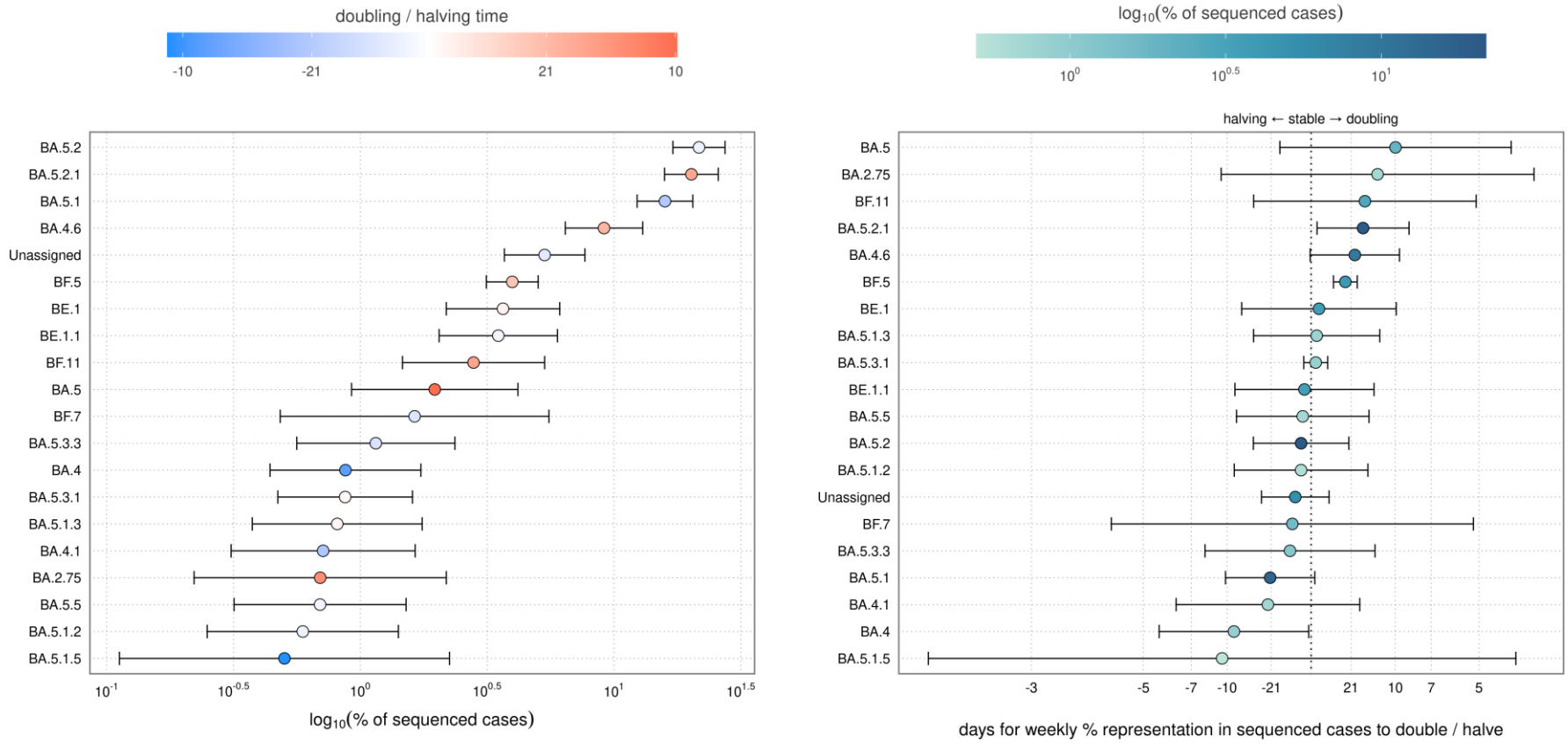
The model suggests that the relative growth rate of BA.4 lineages (other than BA.4.6) is negative, slowly declining as a share of sequenced cases (Table 3). The relative growth rate of BA.5 is stable, with both a slow increase and slow decline in its representation included in confidence intervals (CI). By contrast, BA.4.6 is increasing as a share of sequenced cases,

through slowly. It presently makes up 8.94% (CI: 7.46 to 10.71) of cases. Individual sub-lineages are shown in Figure 8.

Table 3. Modelled relative growth rates (as doubling times) and representation among sequenced cases for BA.4.6, BA.4 and BA.5.

Date of estimate	Variant	Total samples	Modelled Percentage	Relative daily doubling time
30/08/2022	BA.4	7,117	3.33% (CI: 2.14 to 5.19)	-20.5 days (CI: -10.36 to -960.76)
30/08/2022	BA.5	32,529	81.95% (CI: 72.6 to 92.5)	-248.07 days (CI: -53.06 to 92.73)
30/08/2022	BA.4.6	1,187	8.94% (CI: 7.46 to 10.71)	25.35 days (CI: 29.56 to 22.19)

Figure 8. Modelled representation and growth rate (as doubling times) of sequenced Pillar 2 cases in England.



Estimates are for the week ending 4 September 2022. Only variants with 10 or more detections in the last 3 weeks were analysed. Generalised additive models were fit with a negative binomial error structure to counts of cases of a specific variant, using a log-offset term to correct for sampling effort. Data were analysed at the weekly time scale due to sample size constraints. Note that doubling times refer to the weekly representation of variants. Supplementary data are not available for this figure.

1.4 BA.4/BA.5 Severity update

A case-control study examined the risk of being admitted to hospital as an inpatient, among people presenting to emergency care within 14 days of positive test. This compared the risk of admission for those with BA.4 or BA.5 infection against BA.2 infection, the previous dominant variant. Between 16 March 2022 and 23 August 2022, a total of 2,530 people with BA.4 and 12,026 people with BA.5 were compared against 17,022 people with BA.2. The analyses adjusted for age, sex, vaccination status, week of test, and for admissions occurring over the 2 days of extreme heat on 19 and 20 July 2022. After adjustment, there was no difference in the risk of admission between people infected with BA.4 compared to BA.2 (odds ratio: 0.96, 95% CI: 0.86 to 1.08). There was no difference in the risk of admission between people infected with BA.5 compared to BA.2 (odds ratio: 0.97, 95% CI: 0.89 to 1.07).

Part 2. Newly identified Omicron variant: V-22SEP-01 (sub-lineage BA.4.6)

Omicron sub-lineage BA.4.6 was identified as part of horizon scanning on 15 August 2022. On 1 September 2022 BA.4.6 was designated as variant V-22SEP-01 due to an observed increase in growth rate. A new variant definition is being created and will be made available on the UKHSA GitHub variant definitions page.

BA.4.6 is a sub-lineage of variant V-22APR-03 (BA.4), and therefore shares mutations with that variant, but has an acquired mutation in spike: R346T, a site of potential antigenic significance. BA.4.6 represented 3.31% of UK sequences in the week beginning 14 August 2022. As of 5 September 2022, BA.4.6 in England has a logistic growth rate of 36%, relative to the dominant lineage in England, BA.5 (method described in previous briefings).

The earliest sample in GISAID is a genome from Spain, which has a collection date 25 April 2022. To date, a total of 14,181 genomes have been identified from outside the UK, which are assigned to BA.4.6 by Pangolin lineage designation. Countries with sequences in GISAID now include: the United States of America (USA) (9,526), Canada (1,007), Denmark (500), France (400), Australia (288), Germany (248), Chile (242), Dominican Republic (173), Peru (149), Luxembourg (123), Belgium (102), Israel (101), Italy (94), Ireland (93), Sweden (92), Spain (85), Netherlands (84), Brazil (76), Argentina (68), Japan (67), New Zealand (60), Switzerland (54), Puerto Rico (53), South Africa (53), Ecuador (49), Mexico (35), Colombia (34), Trinidad and Tobago (30), Czech Republic (27), Costa Rica (23), Jamaica (21), Portugal (20), South Korea (19), Austria (17), Botswana (17), Indonesia (13), Sint Maarten (12), Senegal (11), and other countries (less than 10 samples) (115). 31 countries had less than 10 BA.4.6 samples.

2.1 Epidemiology

As of 6 September 2022, there were 1,697 cases with BA.4.6 in England.

In England, the first detected BA.4.6 cases had a specimen date of 12 May 2022, in 2 East of England cases. . Most cases (458) were North West residents, with further cases resident in the London (102), West Midlands (181), South East (145), East of England (105) North East (113), South West (141) and Yorkshire and the Humber (197). One hundred and fifty-3 cases have not been assigned a region.

Part 3. Omicron variant: V-22JUL-01 (sub-lineage BA.2.75)

Omicron sub-lineage BA.2.75 was identified as part of horizon scanning on 4 July 2022. BA.2.75 was designated as V-22JUL-01 on 18 July 2022.

The mutation profile for BA.2.75 was previously described in Technical Briefing 44.

The earliest sample in GISAID is a genome from India, which has a sample collection date 26 May 2022. To date, a total of 5,184 genomes have been identified from outside the UK which meet the V-22JUL-01 definition. Countries with sequences meeting the Confirmed or Probable definition in GISAID now include: India (3,574), USA (341), Singapore (252), Australia (186), Japan (135), Canada (118), South Korea (81), Israel (73), Nepal (67), Austria (64), Denmark (54), New Zealand (50), Germany (42), Netherlands (26), Belgium (21), France (17), Russia (11), Indonesia (9), Luxembourg (7), Switzerland (7), Thailand (7), Ireland (6), Malaysia (4), Spain (4), Sweden (4), Portugal (3), Chile (2), Italy (2), Peru (2), Slovakia (2), Brunei (1), Cambodia (1), China (1), Colombia (1), Croatia (1), Finland (1), Iceland (1), Martinique (1), Norway (1), Romania (1), Slovenia (1), South Africa (1), and Turkey (1).

3.1 Epidemiology

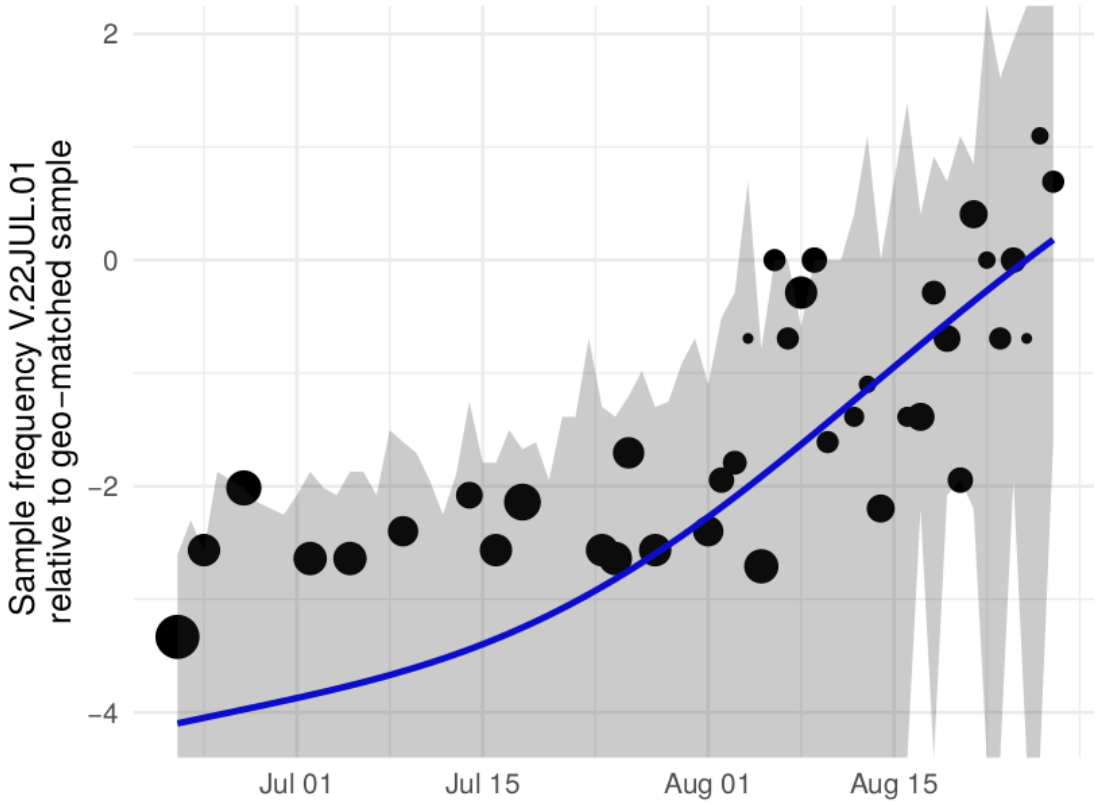
As of 6 September 2022, there were 89 cases with BA.2.75 in England.

In England, the first detected BA.2.75 cases had a specimen date of 20 June 2022, in 2 East of England cases. Most cases (23) were East of England residents, with further cases resident in the London (20), West Midlands (20), South East (7), North West (5) North East (2), South West (2) and Yorkshire and the Humber (1). Seven cases have not been assigned a region. The majority of cases were between 50 and 59 years of age. The median if 53 years of age with an interquartile range of 34-66 years of age.

3.2 Growth rate

The growth rate is estimated by logistic regression of the number of genomes sampled with V-22JUL-01 (BA.2.75) lineages on time of sample collection. Growth rates were based on sequences sampled through Pillar 1 testing in England. To adjust for geographic variation in case growth rates, V-22JUL-01 growth rates were estimated relative to a geographically matched sample of genomes. A logistic growth rate of zero would indicate no difference in growth rates between V-22JUL-01 and other variants. The growth rate increased from July 2022 to August 2022 and is currently 61% per week relative to co-circulating lineages (Figure 9).

Figure 9. Sample frequency of V-22JUL-01 relative to other lineages over time
Supplementary data is not available for this figure



Part 4. VOC-22APR-04 (BA.5)

Omicron sub-lineage BA.5 was identified as part of horizon scanning on 4 April 2022. On 6 April 2022, the Variant Technical Group classified Omicron sub-lineage BA.5 as V-22APR-04. On 18 May 2022, UKHSA re-classified V-22APR-04 as VOC-22APR-04.

The revised genomic case definition for V-22APR-04 is available in Technical Briefing 41.

4.1 Genomic diversity

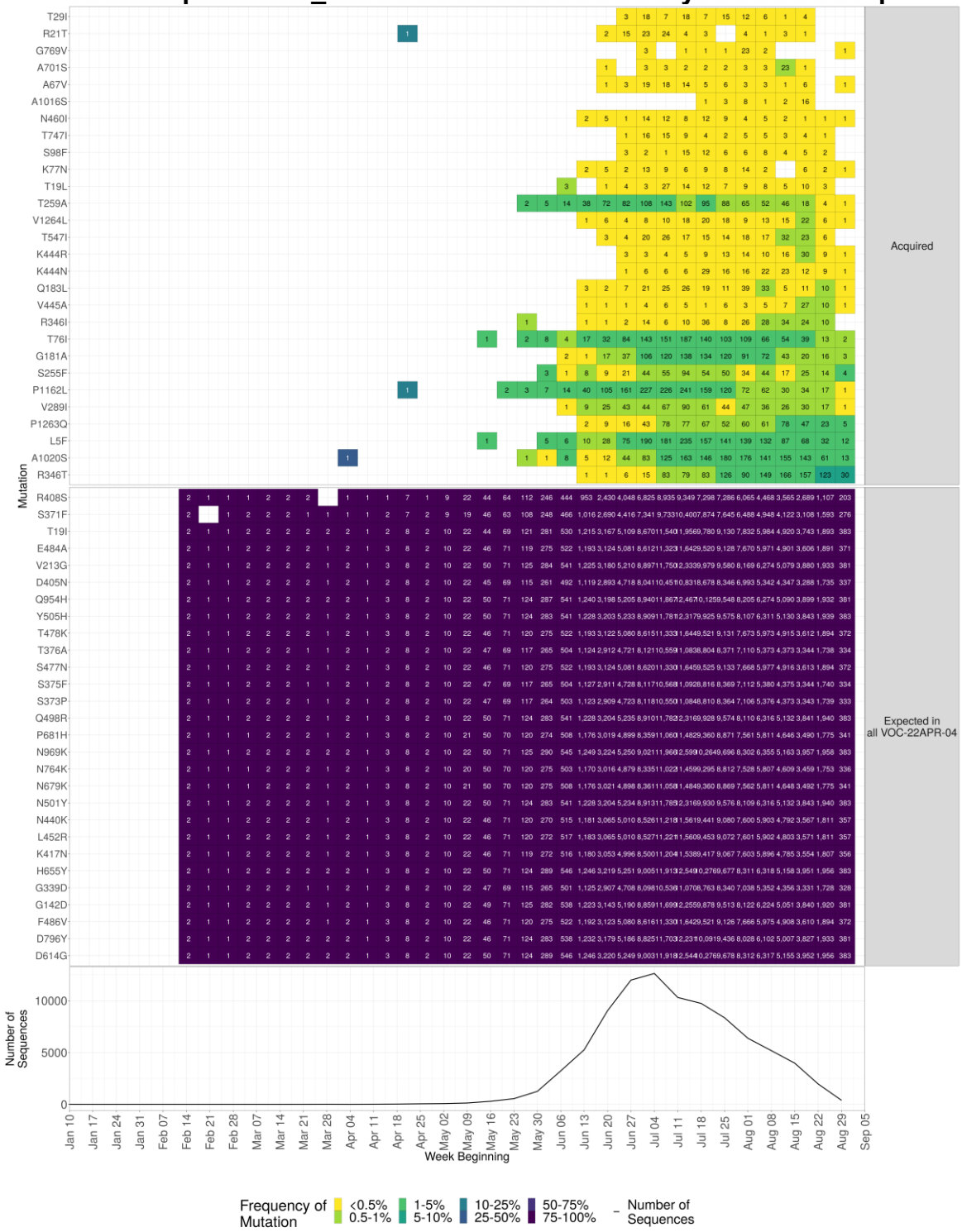
Diversity in Spike

Spike mutations are monitored within VOC-22APR-04 using 4 criteria (Table 4). A mutation is investigated further if it meets more than one of these criteria and is present in at least 10 sequences. Twenty-eight additional mutations have been observed in VOC-22APR-04 sequences according to the criteria in Table 4 (Figure 10). The criteria for mutation monitoring are currently being reviewed and amended.

Table 4. Criteria used to assess emerging mutations

Criteria	Threshold
Cumulative count	Running total for the number of sequences containing mutation is at least 50
Proportion	1% of sequences classified as this variant contain this mutation within a single week
Difference in proportion	The difference in the proportion of sequences in 2 consecutive weeks is at least 0.25%
Percentage change in the number of sequences	The percentage change between the number of sequences containing the mutation in 2 consecutive weeks is at least 5%

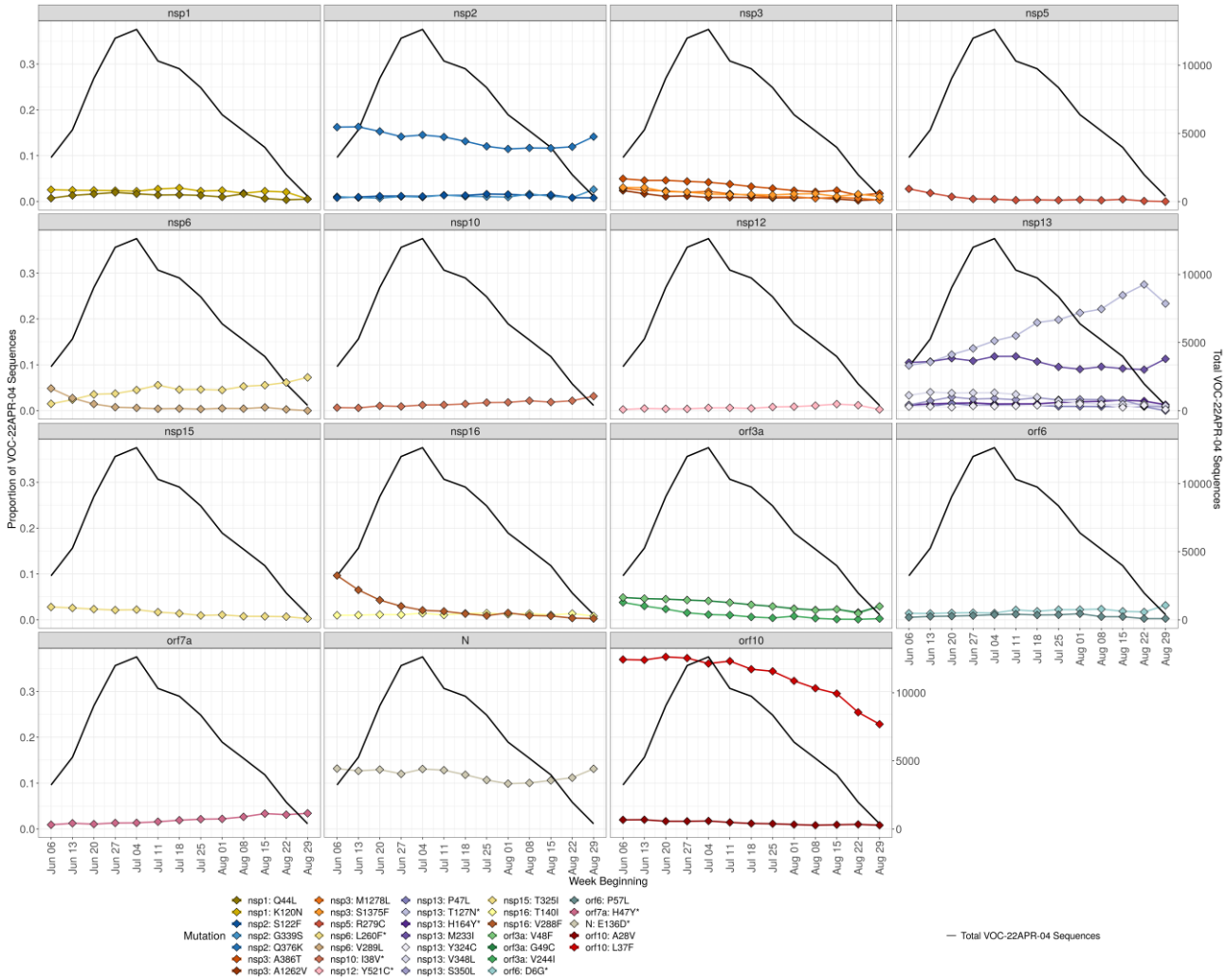
Figure 10. Spike mutations found in VOC-22APR-04 genomes in the UK dataset relative to the Wuhan sequence NC_045512.2 between 10 January 2022 and 4 September 2022



Find accessible data used in this graph in underlying data.
NB: all mutations in the sequence alignment are reported in these plots for review purposes.

Outside of Spike, there are 33 mutations that are present in at least 1% of VOC-22APR-04 sequences for at least 3 consecutive weeks (Figure 11).

Figure 11. Mutations acquired by VOC-22APR-04 outside Spike, shown as a proportion of total VOC-22APR-04 sequences (1 June 2022 and 4 September 2022)



The total number of VOC-22APR-04 sequences per week are indicated by the black line.

Mutations for each genome are called relative to reference Wuhan NC_045512.2 and acquired mutations are those additional to the ancestral BA.5 mutation set. Those that are considered additional, and that are present in at least 1% of BA.5 sequences for at least 3 consecutive weeks in the UK dataset, are included in Figure 11 as a proportion of total BA.5 sequences.

Mutations labelled with (*) are those that have been increasing as a proportion of VOC-22APR-04 sequences for at least 3 consecutive weeks within the previous 6 weeks.

Find accessible data used in this graph in underlying data.

Sources and acknowledgments

Data sources

Data used in this investigation is derived from the COG-UK and UKHSA genomic programme data set, ONS COVID-19 Infection Survey, the UKHSA Second Generation Surveillance System, the Secondary Uses Service data set, Emergency Care Data Set and the UKHSA Case and Incident Management System.

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Matt Holden	Public Health Scotland
Nicholas Loman	UKHSA/University of Birmingham
Richard Myers	UKHSA

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Virology and Immunology	
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Susanna Dunachie	University of Oxford
Tim Wyatt	Northern Ireland Public Health Agency
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Paula Blomquist	UKHSA
Thomas Finnie	UKHSA
Thomas Ward	UKHSA
International epidemiology	
Chris Lewis	Foreign, Commonwealth and Development Office
Nadeem Hasan	Foreign, Commonwealth and Development Office
Katherine Russell	UKHSA
Leena Inamdar	UKHSA

Acknowledgements

The authors are grateful to those teams and groups providing data for these analyses including: the Lighthouse Laboratories, National Health Service, COG-UK, the Wellcome Sanger Institute, Health Protection Data Science teams, the University of Oxford, the Genotype to Phenotype Consortium, Medical Research Council Biostatistics Unit, Cambridge and Imperial College, London.

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

Version 1.0

Published: September 2022
Publishing reference: GOV-13235