UK Health Security Agency

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

Technical briefing 44

22 July 2022

This report provides an update on previous briefings up to 24 June 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 18 July 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 now the predominant circulating variant in the UK.

Newly designated variant – V-22JUL-01 (BA.2.75)

Omicron sub-lineage BA.2.75 was identified as part of horizon scanning on 4 July 2022.

BA.2.75 is a sub-lineage of variant VOC-22JAN-01 (BA.2). It has 33 non-synonymous mutations in Spike. Most of these are shared with other Omicron lineages. Compared to BA.2, this lineage has a reversion in Spike: R493Q, which is also seen in VOC-22APR-03 and VOC-22APR-04. It also contains 8 additional mutations: K147E, W152R, F157L, I210V, and G257S in the N-terminal domain and, G339H, G446S, and N460K in the receptor binding domain. G446S is also seen in BA.1 sequences. G339H is a multi-nucleotide variant and comprises the single nucleotide change seen in BA.2 that causes G339D (22578G>A) plus 22577G>C.

BA.2.75 was designated V-22JUL-01 on 18 July 2022 allowing it to be monitored and investigated once there are sufficient cases.

As of 18 July 2022, there were 24 cases with BA.2.75 in the UK. Of these, 20 were in England, 3 in Scotland and 1 in Wales. It has also been identified in multiple other countries in low numbers.

Published information on variants

On 1 April 2022 the 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) Including Omicron-like variant with additional spike mutations: M153I, T299I, R346K, L368I, E484K, G1219C
Omicron (B.1.1.529) sub-lineage BA.4 VOC-22APR-03	XE Recombinant (BA.1 x BA.2) V-22APR-02	BA.1/BA.2 Recombinant (with unique mutation C3583T)
Omicron (B.1.1.529) sub-lineage BA.5 VOC-22APR-04	V-21OCT-01 (AY.4.2)*	Unassigned Omicron, potential BA.2 recombinant with chronic infection markers: S: M153I, T299I, R346K, L368I, E484K, ntG1219C.
	V-22JUL-01 (BA.2.75)	

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

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)	
	Kappa-VUI-21APR-01 B.1.617.1	

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.

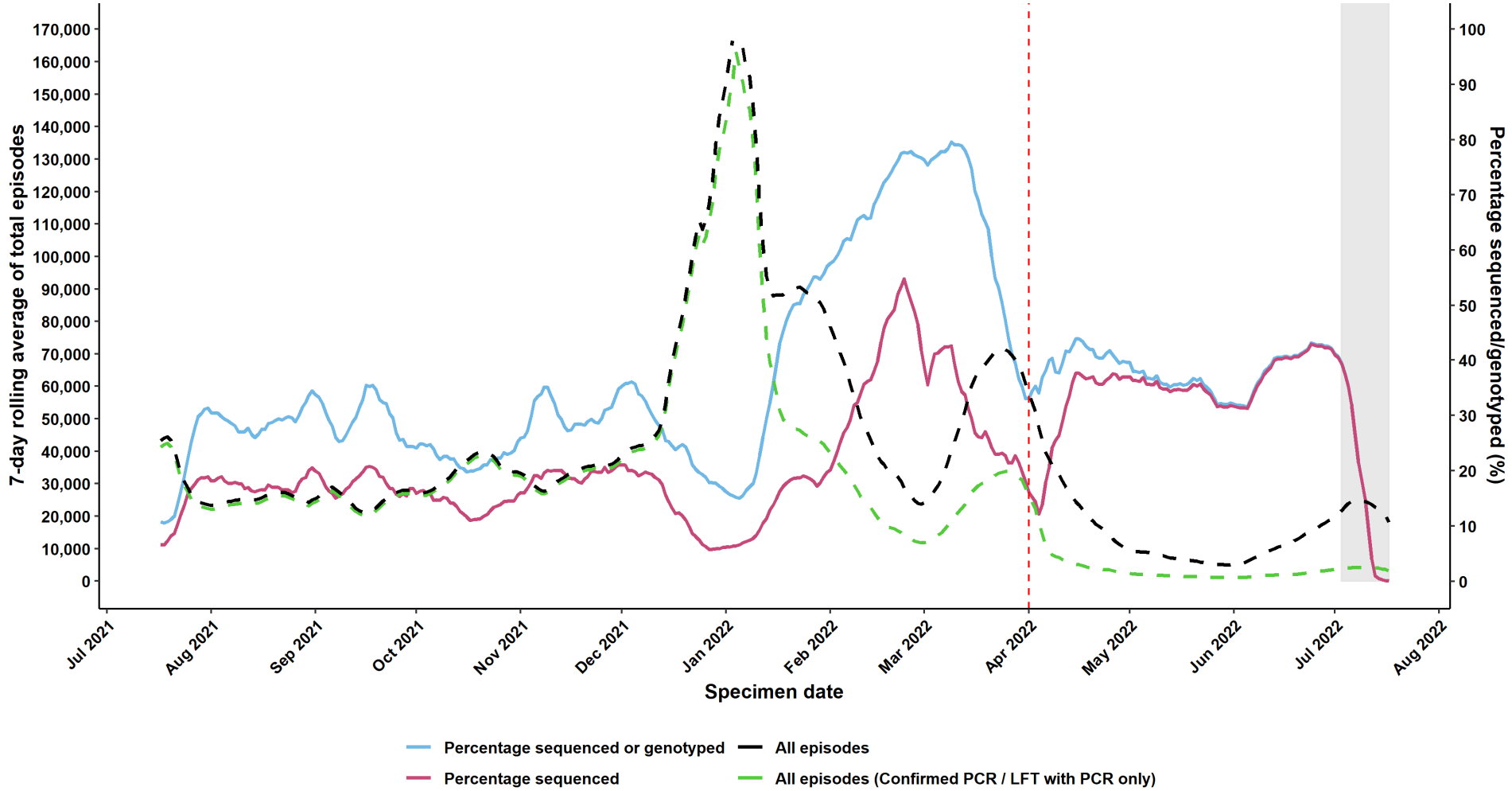
1.1 Sequencing coverage

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.

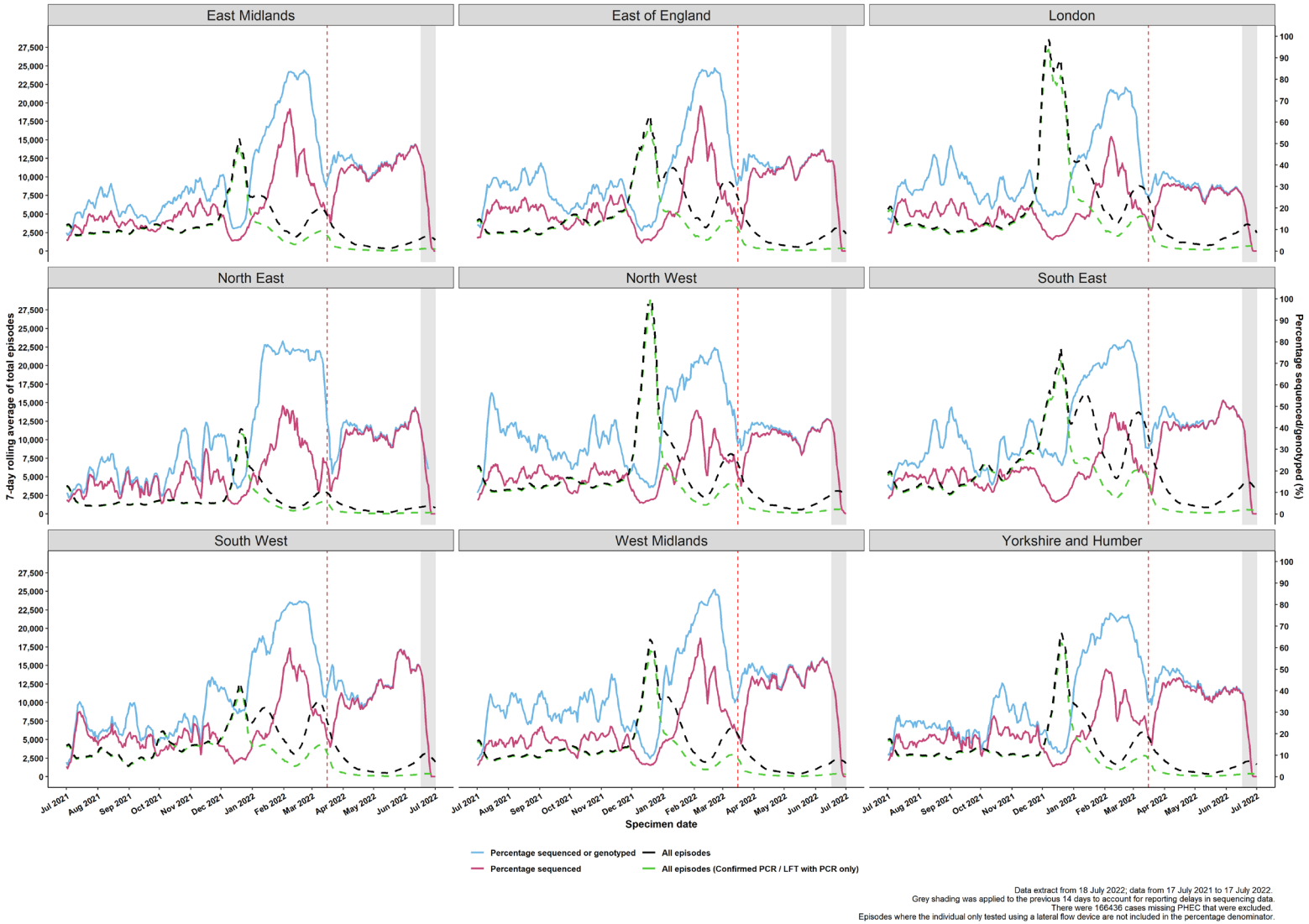
Currently, the sequencing strategy prioritises hospitalised cases, patients who are receiving specific antiviral therapy, and national core priority studies.

Figure 1. Coverage of sequencing with a valid result and genotyping over time (17 July 2021 to 17 July 2022)



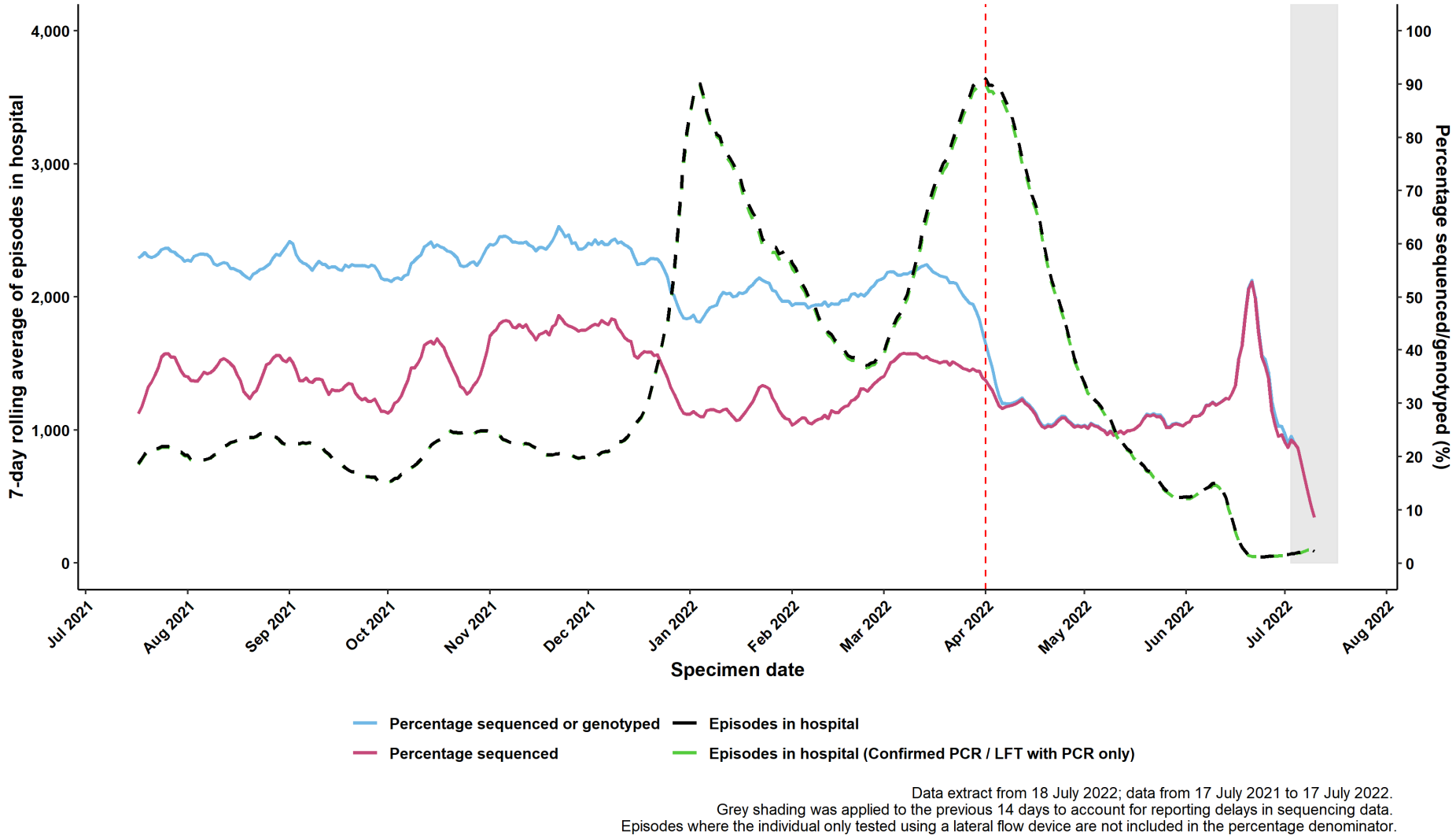
Episodes where the individual only tested using a lateral flow device are excluded. Grey shading was applied to the previous 14 days to account for reporting delays in sequencing data. (The data used in this graph can be found in the accompanying spreadsheet.)

Figure 2. Coverage of sequencing with a valid result and genotyping over time by region (17 July 2021 to 17 July 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 (17 July 2021 to 17 July 2022)

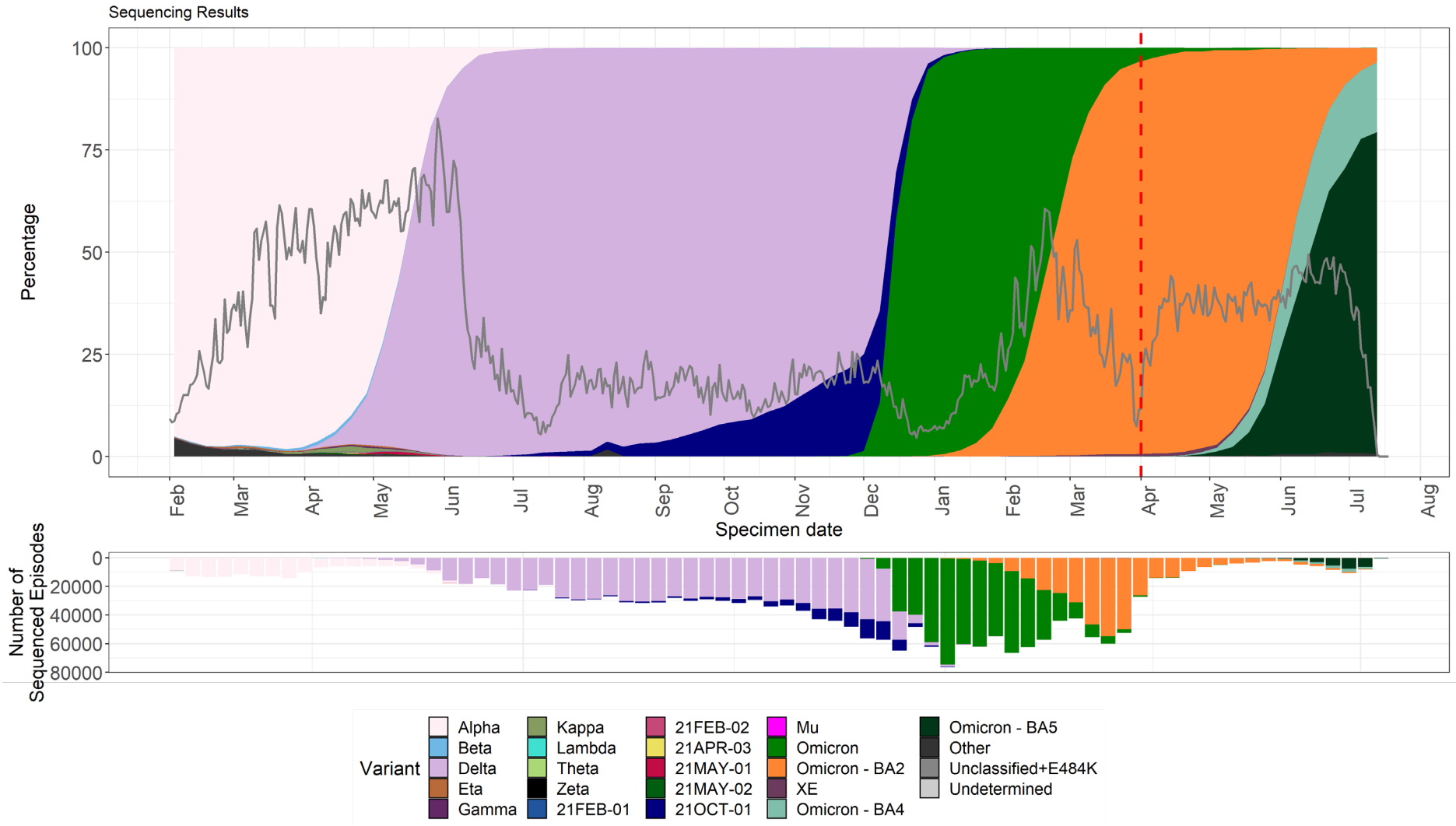


Episodes where the individual only tested positive using a lateral flow device are excluded. Grey shading was applied to the previous 14 days to account for reporting delays in sequencing data. (The data used in this graph can be found in the accompanying spreadsheet.)

1.2 Variant prevalence

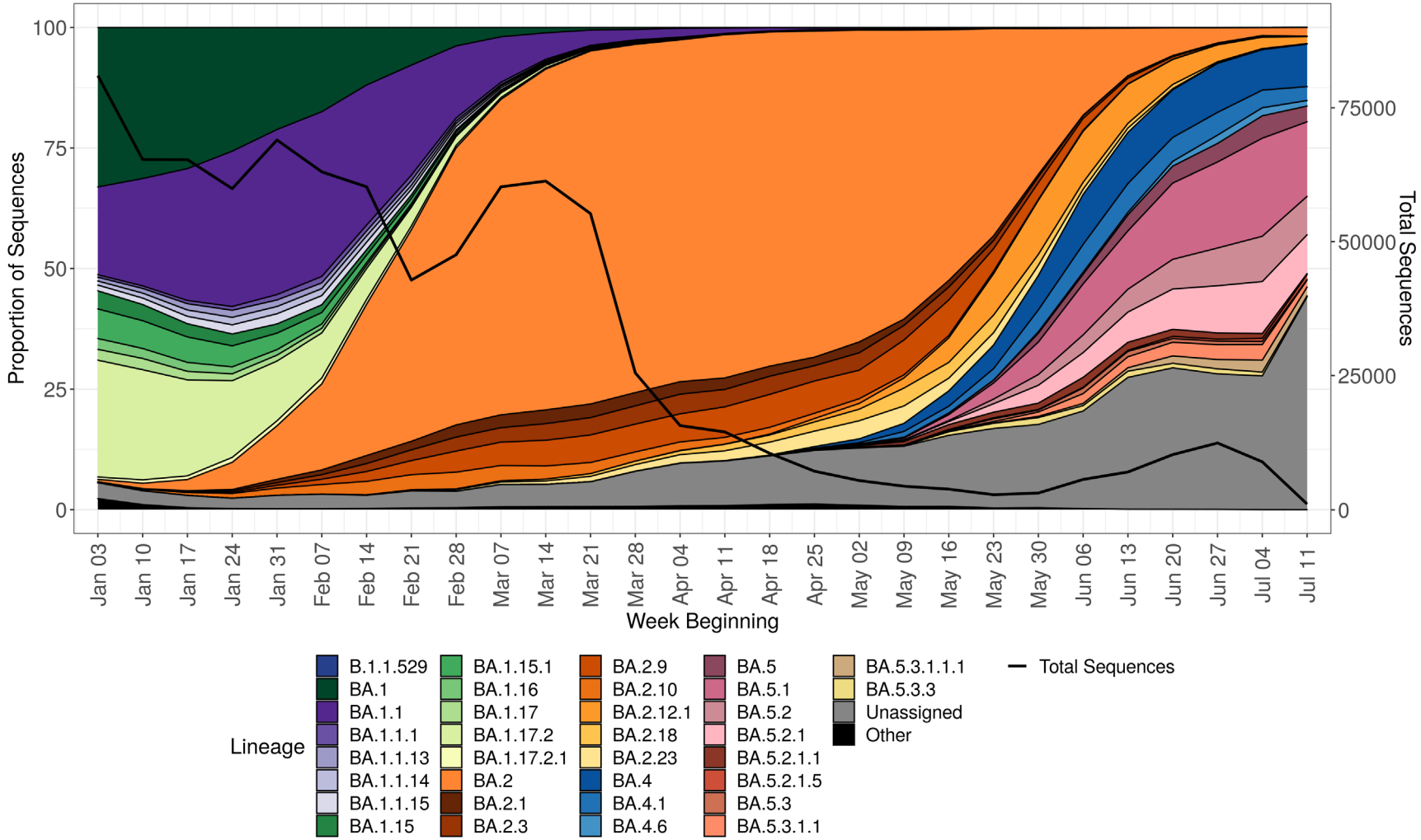
The prevalence of different UKHSA-designated variants amongst sequenced episodes is presented in Figure 4 and by Pangolin designation in Figure 5. Of the sequenced episodes from 10 July 2022 to 17 July 2022, 3.4% were BA.2 (VOC-22JAN-01) 17.2% BA.4 (VOC-22APR-03), 78.7% BA.5 (VOC-22APR-04) and 0.7% were classified as other.

Figure 4. Variant prevalence of available sequenced episodes for England from 1 February 2021 as of 18 July 2022



Find accessible data used in this graph in underlying data. Dashed lines indicate period incorporating issue at a sequencing site. The 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 17 July 2022



The total number of valid sequence results per week is shown by the black line. Lineages are shown if there are >= 5000 sequences since 3 January 2022 or if they are >=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). 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.

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. Of the 12,508 sequences that are unassigned by Pangolin since 6 June 2022, UKHSA variant classifications define 9,115 (72.87%) as VOC-22APR-04, 1,255 (10.03%) VOC-22APR-03, 786 (6.28%) VOC-22JAN-01, 1 (0.01%) VOC-21NOV-01, and 1,264 (10.11%) 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.

1.3 Variant modelling

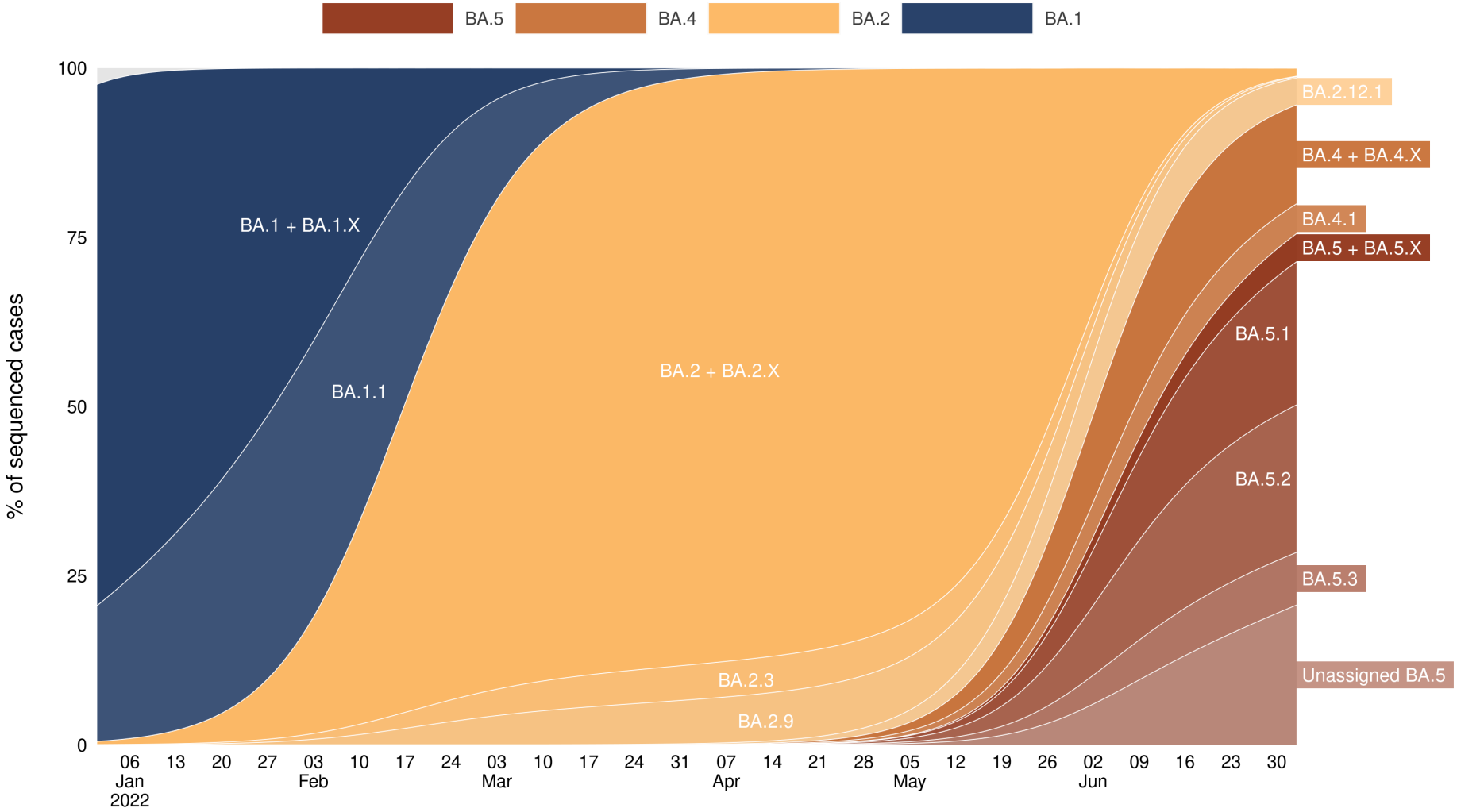
Multinomial model

A Bayesian multinomial model was used to describe the dynamics of Omicron lineages in England between 1 January 2022 and 3 July 2022, with the objective of determining which BA.5, BA.4 or BA.2 lineage had the largest relative fitness advantage.

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). We omit the small (less than 5%) of samples that could not be assigned to even a parent lineage. Unassigned BA.5 lineages are samples that could not be allocated a specific BA.5 sub-lineage but could be confirmed as BA.5. These unassigned BA.5 samples are therefore likely an amalgam of emerging BA.5 sub-lineages that are difficult to define. Whilst this is an imprecise approach, it can be used as an early horizon scanning tool for sub-lineages with potential growth advantages which can trigger phenotypic studies and epidemiological assessment.

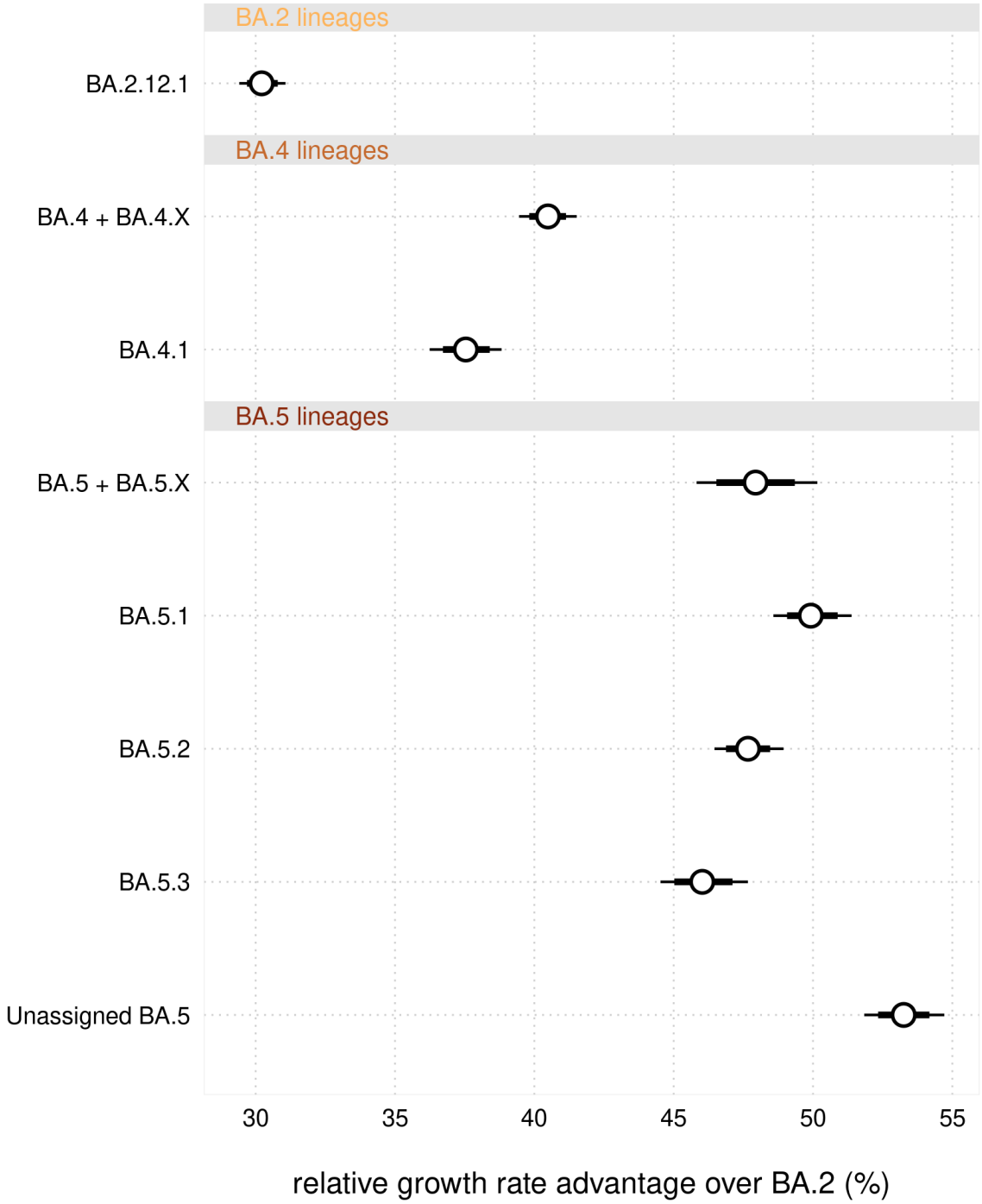
The modelled percentage representation is shown in Figure 6 and the estimated relative growth rates for each Omicron lineage is given in Figure 7. This model suggests that BA.5 has the largest relative fitness advantage, followed by BA.4 then BA.2.12.1 (Figure 7). Unassigned BA.5 samples had the largest growth advantage among BA.5 lineages, but this is likely an artefact of the class combining several, difficult to classify, sub lineages. It is also possible that the growth rates of BA.5.2 and BA.5.3 lineages are impacted by their classification as ‘unassigned’. Table 2 gives the estimated percentages for each emerging lineage.

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 Delta lineages that were on the decline entering 2022. Supplementary data is not available for this figure.

Figure 7. Estimated relative growth rates for emerging BA.5, BA.4 and BA.2 lineages from a multinomial model of sequenced cases in England



The relative growth rates are taken from a multinomial model of sequenced cases. 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 the 3 of July 2022

Lineage	%	Upper CrI	Upper CrI	Parent lineage total
Unassigned BA.5	20.64	19.85	21.43	75.53
BA.5.3	7.78	7.3	8.28	N/A
BA.5.2	21.79	21	22.58	N/A
BA.5.1	21.16	20.4	22.01	N/A
BA.5 + BA.5.X	4.16	3.8	4.55	N/A
BA.4.1	4.41	4.1	4.74	19.03
BA.4 + BA.4.X	14.62	14.03	15.22	N/A
BA.2.12.1	3.97	3.72	4.25	5.42
BA.2.9	0.18	0.16	0.2	N/A
BA.2.3	0.09	0.09	0.1	N/A
BA.2 + BA.2.X	1.18	1.1	1.26	N/A

Relative growth rates

The representation of different lineages among sequenced cases was modelled for the last 3 months in England. 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.

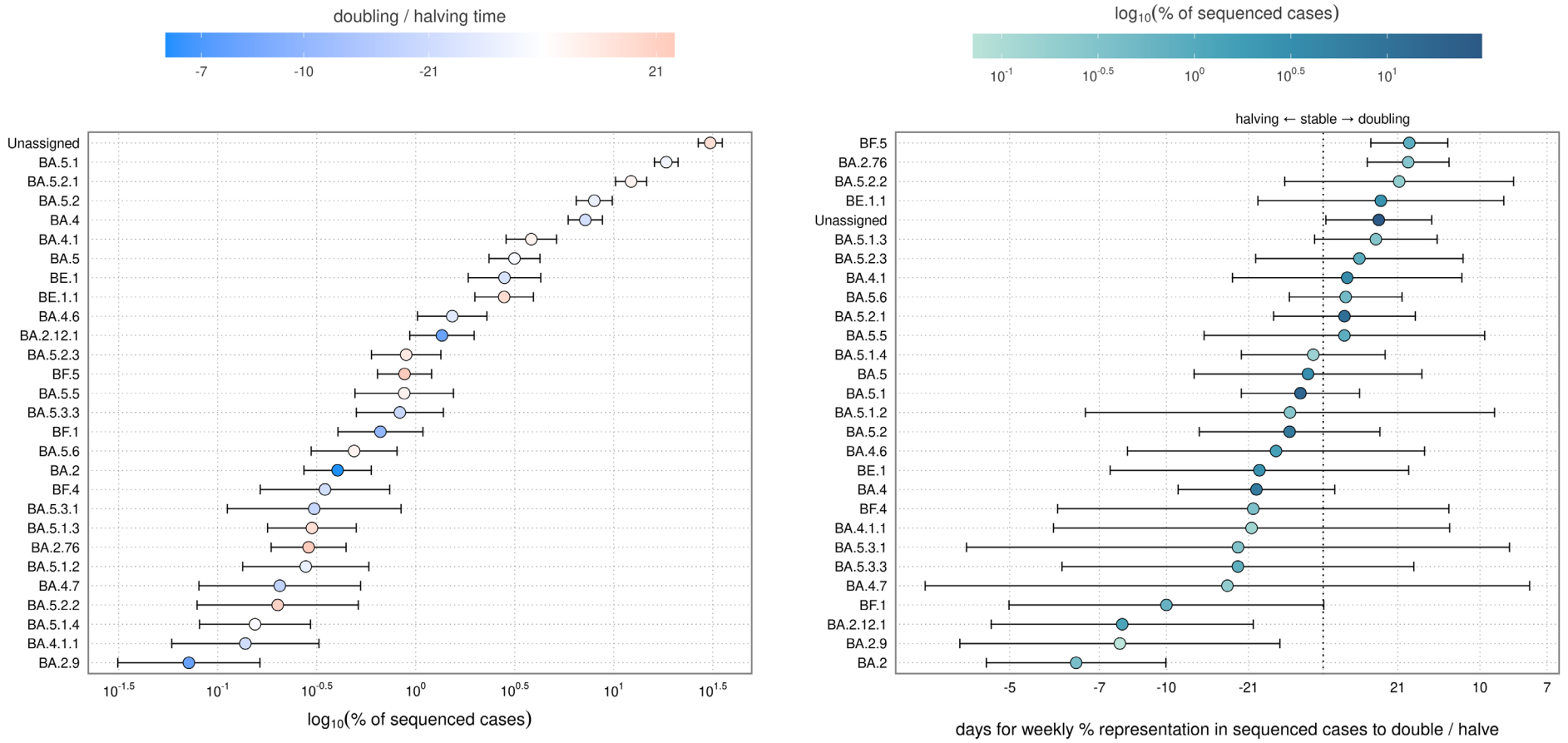
We fit models both the weekly timescale by lineage (due sample sizes) and on the daily timescale by coarser definitions (BA.5, BA.4, BA.2.12.1, BA.2 excluding 12.1, BA.1 and ‘other’). For the weekly timescale, only variants that were sequenced 10 or more times in the past 2 weeks are included (Figure 8). Estimates are for the 13 July 2022. The 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.2.12.1 and BA.4 are both in decline (Table 3). The relative growth rate of BA.5 has slowed considerably, but its representation is likely still increasing. It is likely that the slowing in BA.5 is due both to it saturating as the dominant variant (relative growth will always eventually saturate) and misclassification of BA.5 as ‘other’. Individual sub lineages are shown in Figure 8.

Table 3. Modelled relative growth rates (as doubling times) and representation among sequenced cases for BA.2.12.1, BA.4 and BA.5

Date of estimate	Variant	Total samples	Percentage	Relative doubling time
13/07/2022	BA.2.12.1	1,974	1.46% (CI: 1.08 to 1.96)	-8.87 days (CI: -6.69 to -13.17)
13/07/2022	BA.4	5,661	14.51% (CI: 12.23 to 17.22)	-25.8 days (CI: -16.05 to -65.74)
13/07/2022	BA.5	16,286	82.92% (CI: 78.34 to 87.76)	45 days (CI: 75.11 to 32.12)

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



Estimates are for the week ending 17 July 2022. Only variants with 10 or more detections in the last 2 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 was 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 Update on the SARS-CoV-2 Immunity and Reinfection EvaluatioN (SIREN) a cohort study in healthcare workers

The SARS-CoV-2 Immunity and Reinfection EvaluatioN (SIREN) is a cohort over 44,000 National Health Service healthcare workers, recruited from 135 hospital sites UK-wide. Participants under active follow-up undergo asymptomatic SARS-CoV-2 PCR testing every 2 weeks. This cohort had high seropositivity on recruitment (30% before the second wave) and is now highly vaccinated (more than 95%). The incidence of new infections and potential reinfections in SIREN is monitored.

Reinfections were defined as a new PCR positive infections 90 days after a previous PCR positive date or 28 days after antibody positivity consistent with prior infection. Monthly primary infection rate calculated as primary infection detection in the month divided by the number of participants undergoing PCR testing with the month. Monthly reinfection rate calculated as reinfections detected in the month divided by the number of participants in the positive cohort undergoing PCR testing within the month. Positive cohort status was calculated at the beginning of each month.

Figure 9 shows the fortnightly trend in PCR positivity in the SIREN cohort. PCR positivity has increased since mid-May. Figure 10 shows the rate of primary infections and reinfections in the SIREN cohort have increased since mid-May and throughout June 2022.

Figure 9. Fortnightly trends in PCR positivity in the SIREN study, June 2020 to July 2022
Supplementary data is not available for this figure.

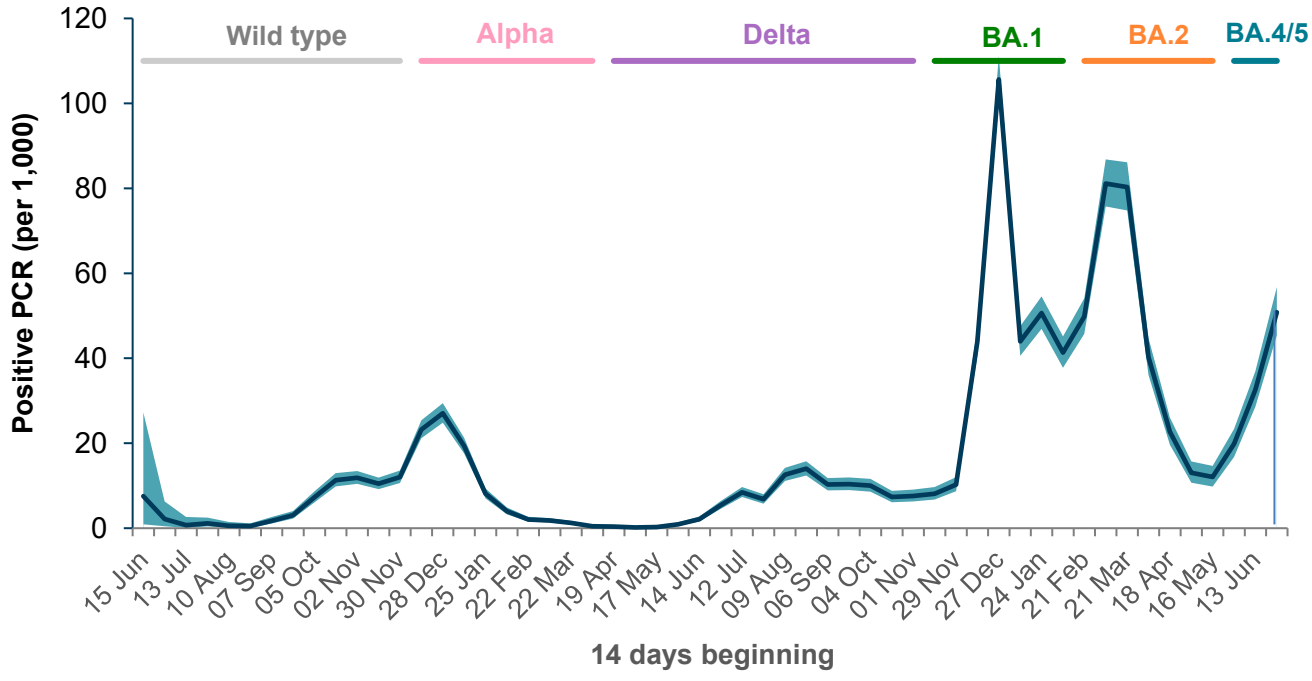
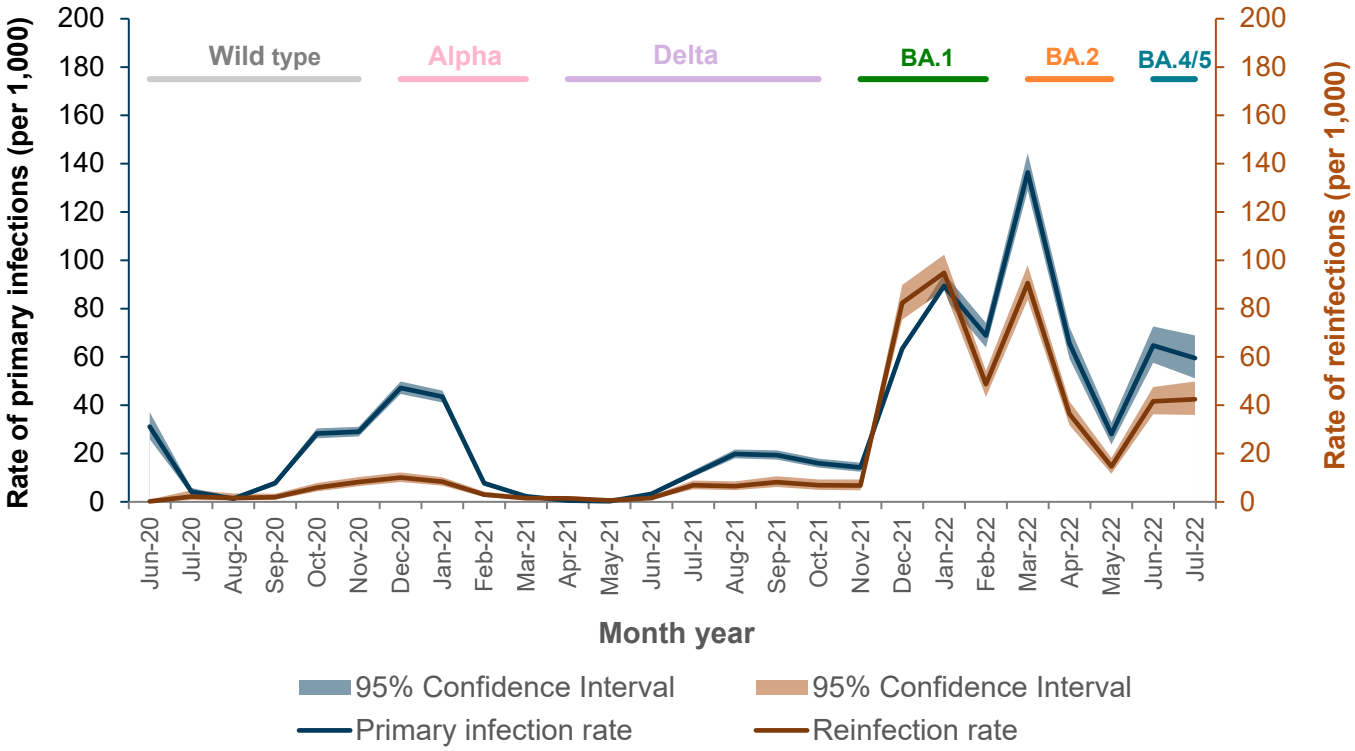


Figure 10. Rate of primary infection (per 1,000 tests in those without prior infection) and reinfections (per 1,000 test in those with prior infection) in SIREN participants per month in the UK, June 2020 to July 2022

Supplementary data is not available for this figure.



Part 2. Newly identified Omicron sub-lineage: V-22JUL-01 (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.

BA.2.75 is a sub-lineage of variant VOC-22JAN-01 (BA.2) and therefore shares mutations with that variant, but has a reversion in Spike: R493Q, which is also seen in VOC-22APR-03 and VOC-22APR-04. The current definition for V-22JUL-01 can be found in the variant definitions GitHub. The mutations included are shown in Table 4. Genomically confirmed sequences require at least 7 out of 10 mutations and cannot contain any reference calls at the positions of interest (allowed_wildtype = 0). Genomically Probable sequences require at least 4 of 10 mutations and can contain up to 2 reference calls (allowed_wildtype = 2).

Table 4. Mutations included in the V-22JUL-01 variant definition. Note these are not all the mutations found in this variant, only those that are a defining combination. Where an amino acid change is not given, the mutation is a synonymous change

Position	Reference Base	Alternate Base	Amino Acid Change
3796	C	T	-
3927	C	T	NSP3: S403L
4586	C	T	-
5183	C	T	NSP3: P822S
12444	A	G	NSP8: N118S
22190	A	G	S: I210V
22331	G	A	S: G257S
22577	GG	CA	S: G339H
22942	T	G	S: N460K
26275	A	G	E: T11A

The earliest sample in GISAID is a genome from India, which has a sample collection date 26 May 2022. To date, a total of 268 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 Australia (2), Canada (4), Denmark (1), Germany (2), India (227), Indonesia (3), Japan (5), Luxembourg (1), Martinique (1), Nepal (1), Netherlands (1), New Zealand (6), Turkey (1), United States (13).

2.1 Epidemiology

As of 18 July 2022, there were 24 cases with BA.2.75 in the UK. Of these, 20 were in England, 3 in Scotland and 1 in Wales. In England, the first detected BA.2.75 cases had a specimen date of 20 June 2022, in 2 East of England cases (Figure 11). Most cases (13) were London residents, with further cases resident in the East of England (3), West Midlands (2), North East (1), and North West (1) of England. The majority of cases were between 20 and 39 years of age (Figure 12), with a median age of 30 (IQR 22.5 to 39.5) years.

Figure 11. Regional epicurve of the 20 sequenced BA.2.75 cases from England by specimen date and region of residence, data as of 18 July 2022

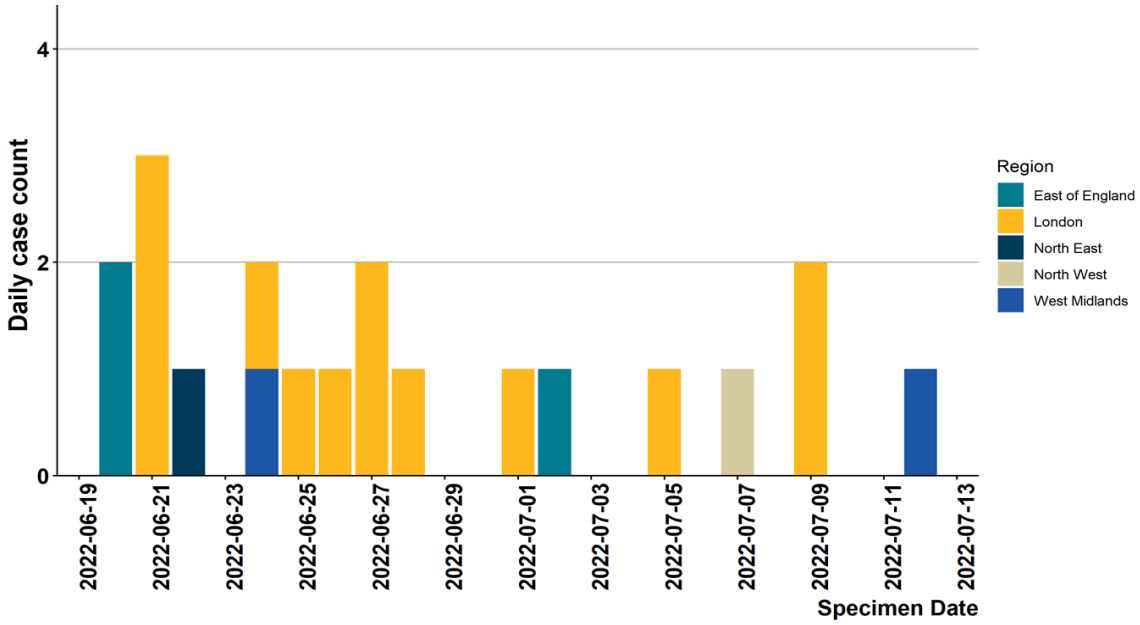
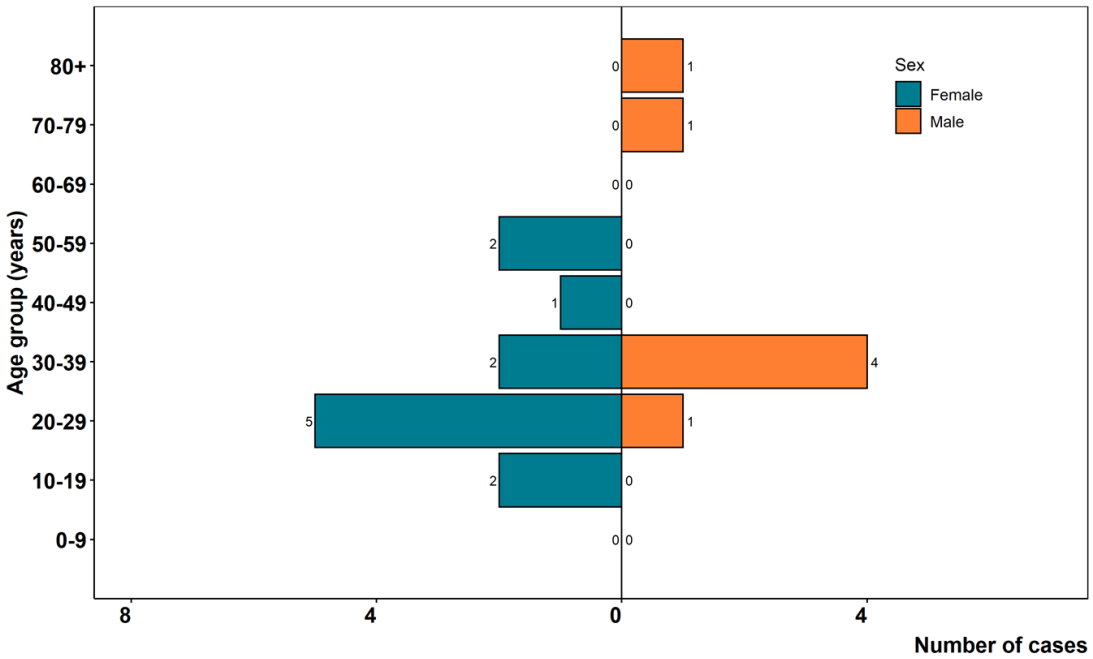


Figure 12. Age-sex pyramid of BA.2.75 cases in England, data as of 18 July 2022.
One case missing information on age and sex.



Part 3. 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.

3.1 Genomic diversity

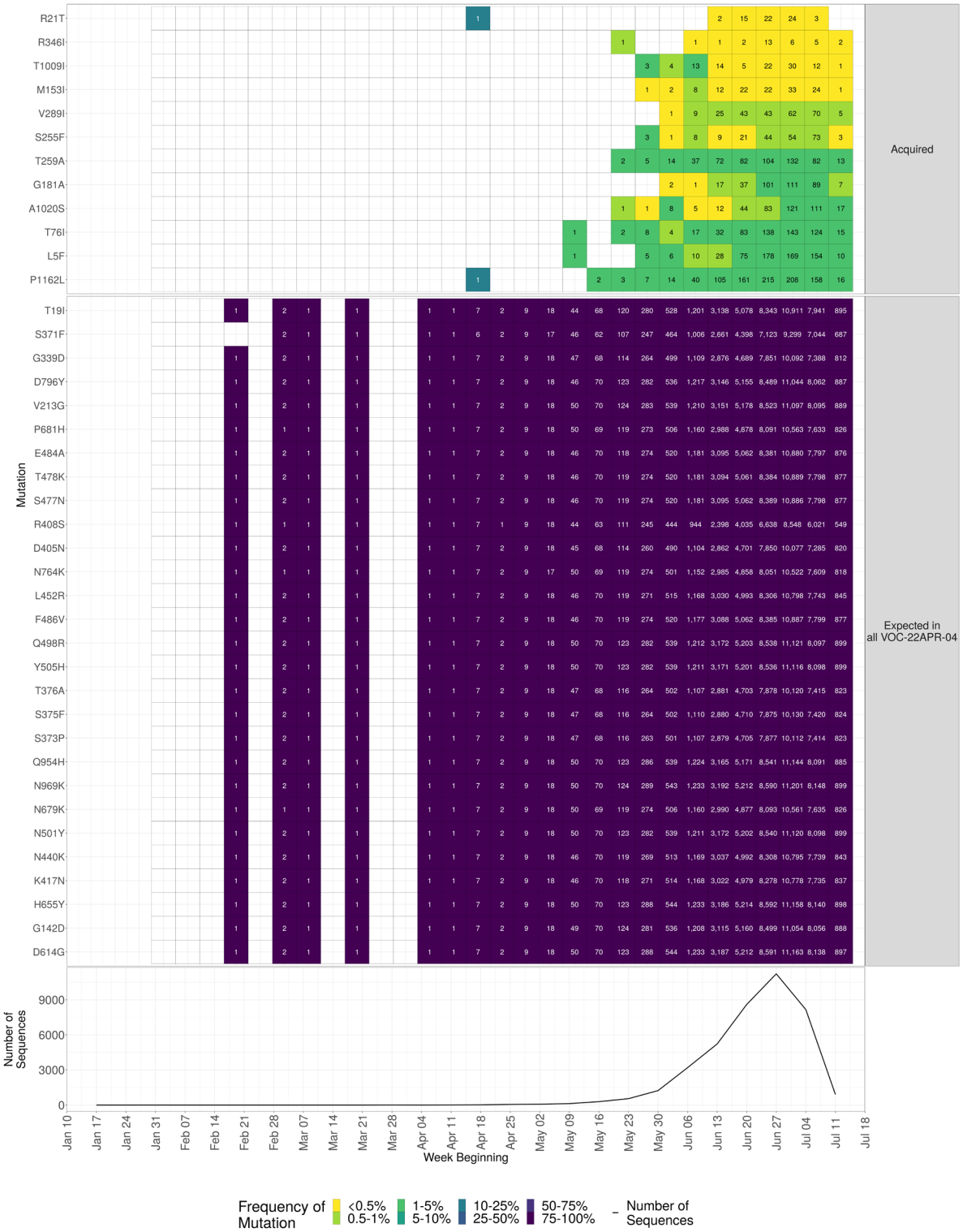
Diversity in Spike

Spike mutations are monitored within VOC-22APR-04 using 4 criteria (Table 2). A mutation is investigated further if it meets more than one of these criteria and is present in at least 10 sequences. Twelve additional mutations have been observed in VOC-22APR-04 sequences according to the criteria in Table 2 (Figure 13). The criteria for mutation monitoring are currently being reviewed and amended.

Table 2. 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%

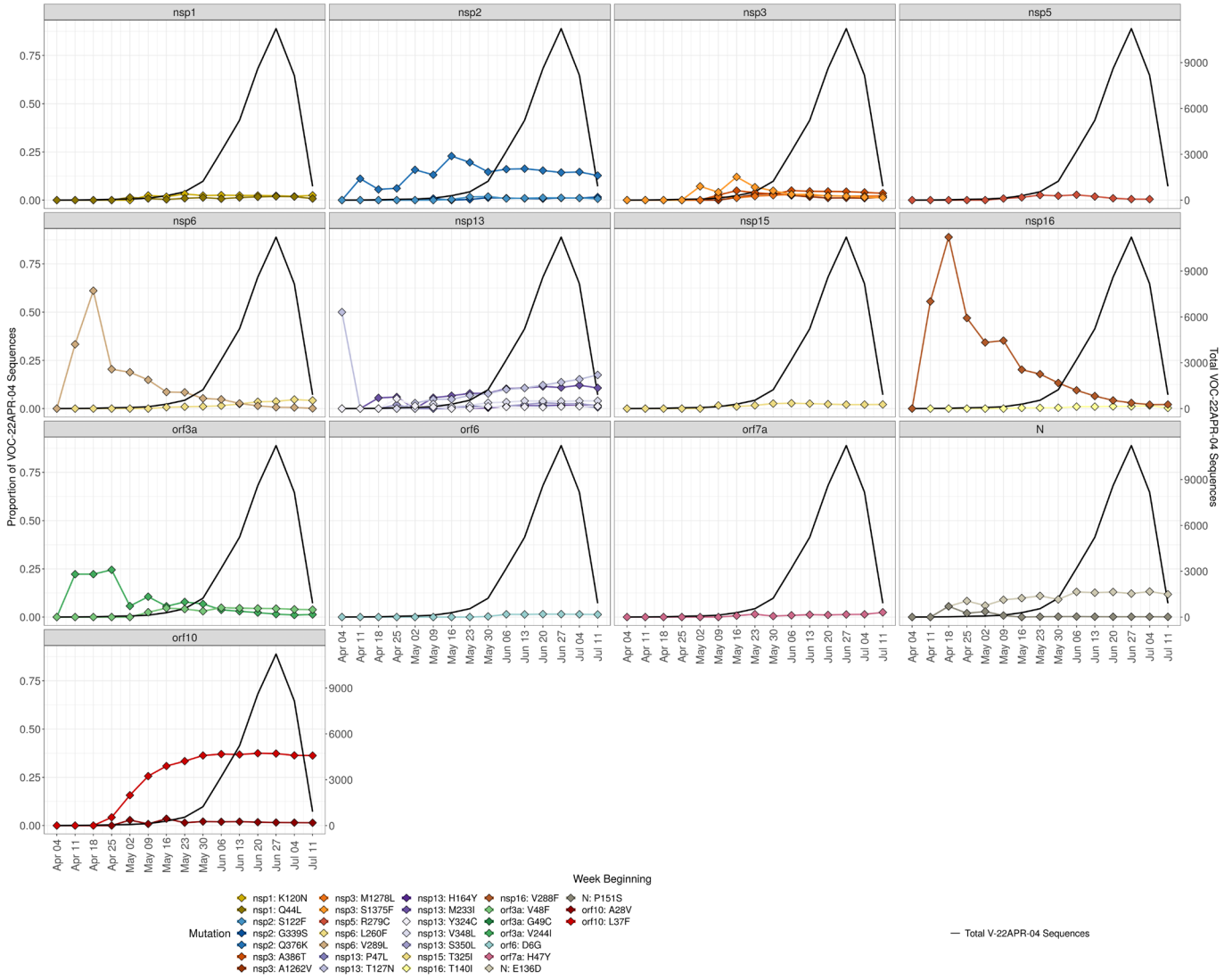
Figure 13. Spike mutations found in VOC-22APR-04 genomes in the UK dataset relative to the Wuhan sequence NC_045512.2 between 10 Jan 2022 and 19 July 2022



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 31 mutations that are present in at least 1% of VOC-22APR-04 sequences for at least 3 consecutive weeks (Figure 14).

Figure 14. Mutations acquired by VOC-22APR-04 outside Spike, shown as a proportion of total VOC-22APR-04 sequences (1 April 2022 and 19 July 2022)



The total number of VOC-22APR-04 sequences per week is 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 data set, are included in Figure 14 as a proportion of total BA.5 sequences.

Mutations labelled with an asterisk (*) are those that have been increasing as a proportion of VOC-22JAN-01 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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UKHSA Surveillance Team

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UKHSA Infectious Disease Modelling Team

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

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Lance Turtle	University of Liverpool
Maria Zambon	UKHSA
Ravi Gupta	University of Cambridge
Susanna Dunachie	University of Oxford
Tim Wyatt	Northern Ireland Public Health Agency
Thushan da Silva	University of Sheffield
Wendy Barclay	Imperial College London
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