UK Health Security Agency

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

Technical briefing 42

20 May 2022

This report provides an update on previous briefings up to 6 May 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 16 May 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.

VOC-22JAN-01 (Omicron sub-lineage BA.2)

VOC-22JAN-01 remains dominant in the United Kingdom (UK) based on sequencing data. Some diversity is developing within this variant, based on both lineage and mutation surveillance.

VOC-22APR-03 (Omicron sub-lineage BA.4) and VOC-22APR-04 (Omicron sub-lineage BA.5)

Updated growth modelling suggests BA.4 and BA.5 are likely to have a growth advantage over BA.2, including within the UK. This is based on small numbers of cases and there is a high degree of uncertainty. However, together with the laboratory data suggesting some degree of immune escape, BA.4 and BA.5 have been designated Variants of Concern, as this classification is intended to provide an early warning of potential risk of increased community transmission. There is no data to determine the impact of these variants on the hospital admissions in the UK.

Published information on variants

On 1 April 2022 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 VOCs and VUIs up to 25 March 2022. The latest COVID-19 variants: genomically confirmed case numbers are published on Gov.uk.

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 variants under investigation (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-21OCT-01 (AY.4.2) †	BA.3
Omicron (B.1.1.529) sub-lineage BA.2 and descendant lineages VOC-22JAN-01	Alpha (B.1.1.7) V-20DEC-01	Delta and Omicron recombinant lineages (UK)
Omicron (B.1.1.529) sub-lineage BA.4 VOC-22APR-03	Delta (B.1.617.2 and sub-lineages) V-21APR-02	BA.1/BA.2 Recombinant (with unique mutation C3583T)
Omicron (B.1.1.529) sub-lineage BA.5 VOC-22APR-04	XE Recombinant (BA.1 x BA.2) V-22APR-02	XF Recombinant
		BA.2.12.1

† 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
Beta (B.1.351) V-20DEC-02	V-21FEB-03 B.1.525 (Formerly Eta)	AY.119.2/BA.1.1 Recombinant
	XD Recombinant (Delta x BA.1) V-22APR-01	

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 Variants 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.

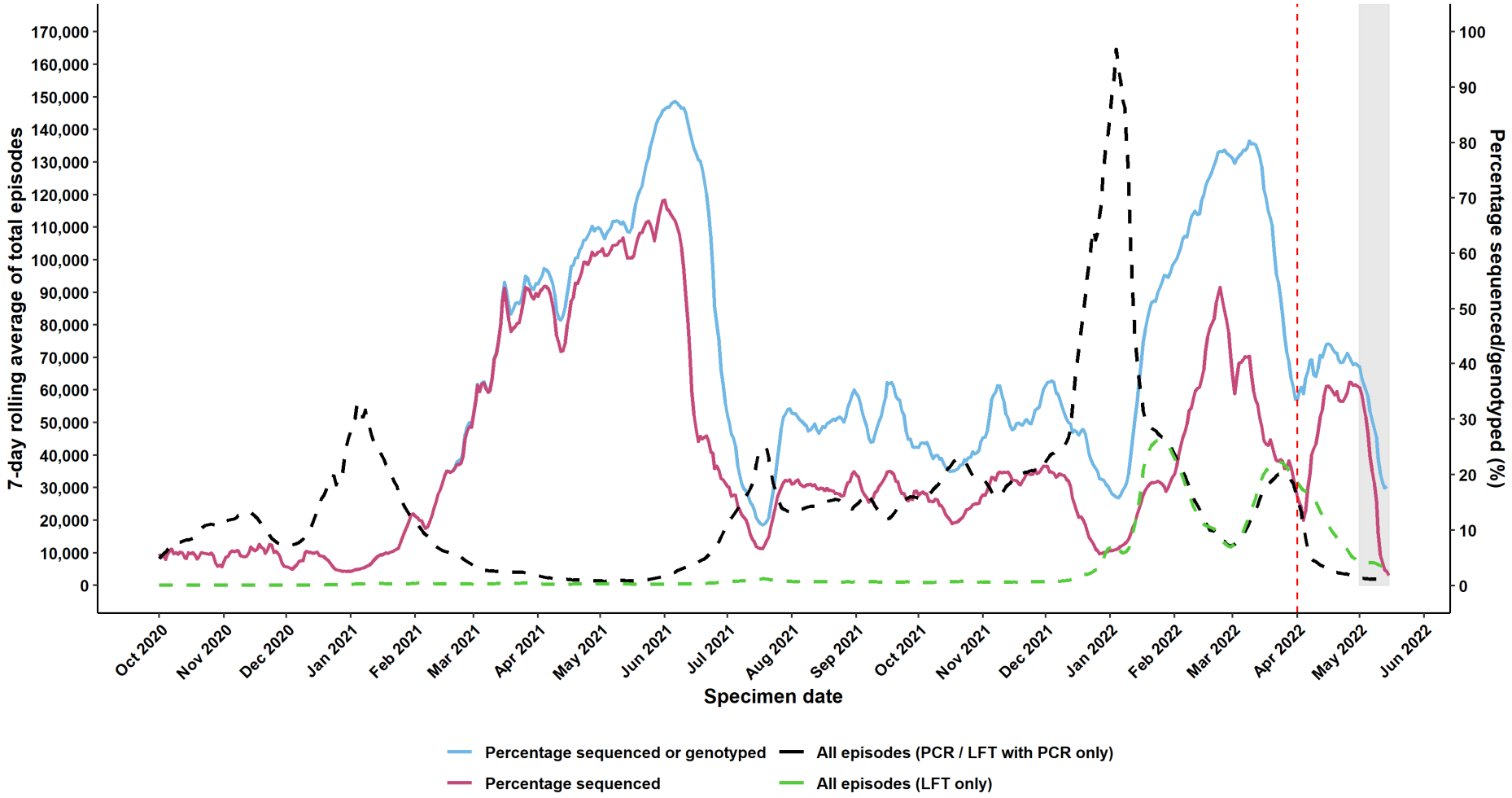
1.1 Sequencing coverage

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.

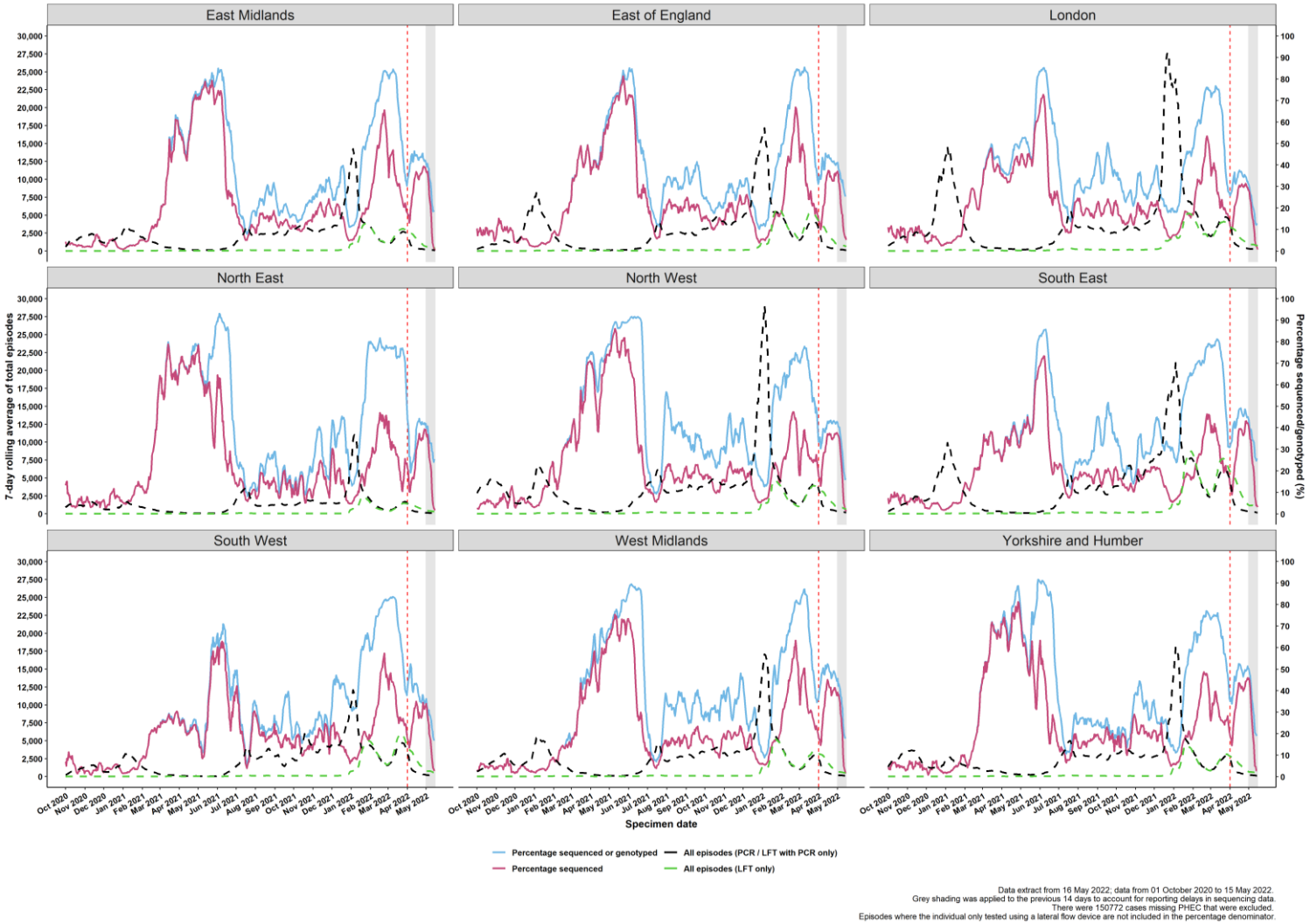
Figure 1. Coverage of sequencing with a valid result and genotyping over time (1 October 2020 to 16 May 2022)



Data extract from 16 May 2022; data from 01 October 2020 to 15 May 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.

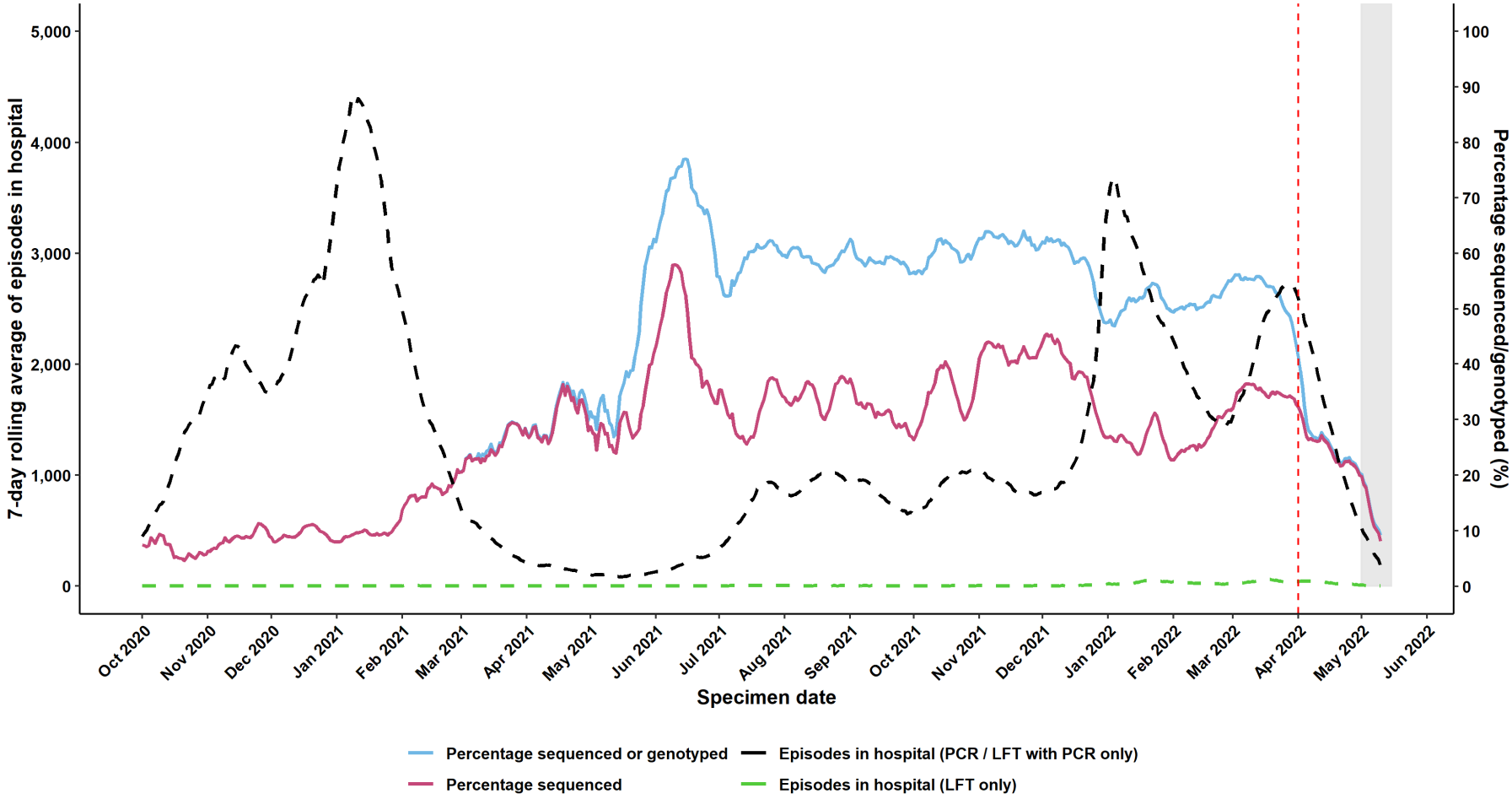
Episodes where the individual only tested using a lateral flow device are excluded. Grey shading was applied to the previous 14 days to account for reporting delays in sequencing data. (The data used in this graph can be found in the accompanying spreadsheet.)

Figure 2. Coverage of sequencing with a valid result and genotyping over time by region (1 October 2020 to 16 May 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 (1 October 2020 to 16 May 2022)



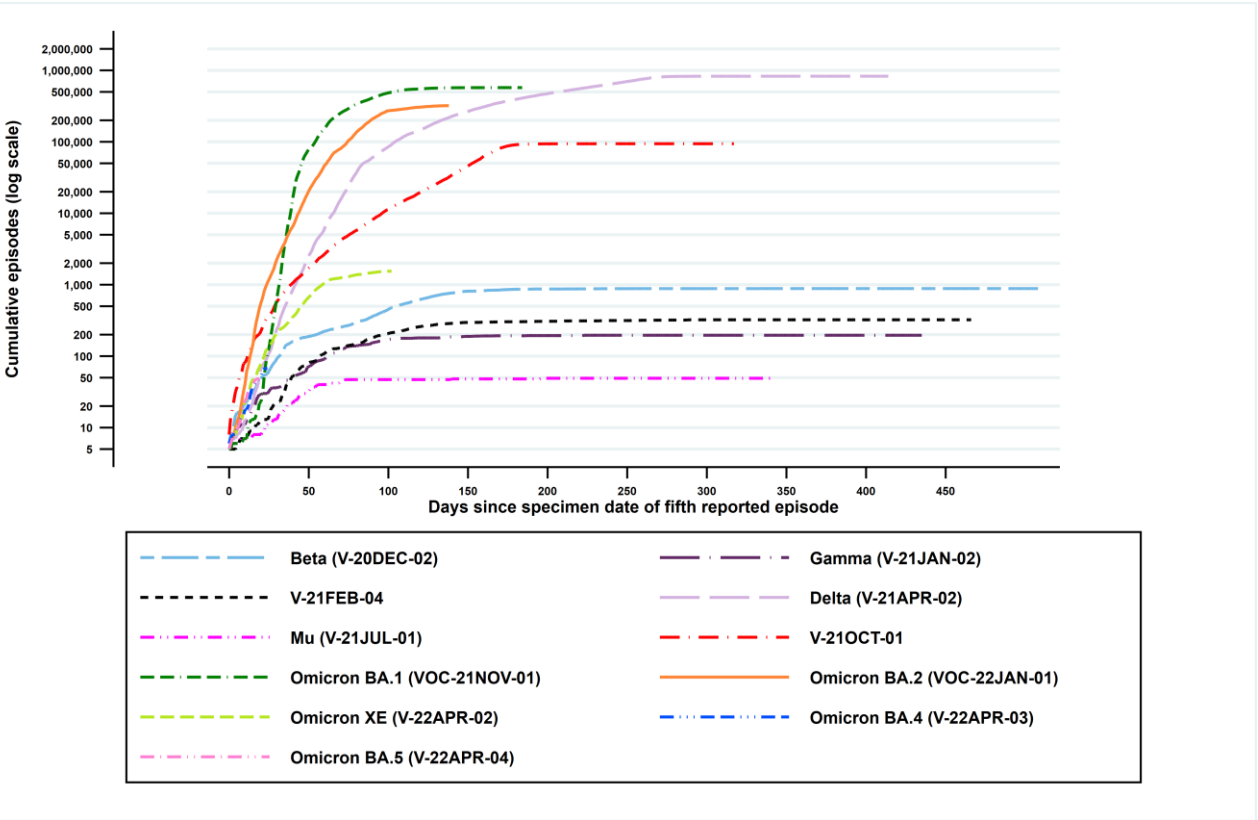
Data extract from 16 May 2022; data from 01 October 2020 to 15 May 2022.
Grey shading was applied to the previous 14 days to account for reporting delays in sequencing data.
Episodes where the individual only tested using a lateral flow device are not included in the percentage denominator.

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 VOC and variant overview

Summary epidemiology for each variant and episode numbers are updated online. Figure 4 shows the cumulative number of episodes (whole genome sequenced only) per variant indexed by days since the first report.

Figure 4. Cumulative episodes* in England of variants indexed by days since the fifth reported episode as of 16 May 2022



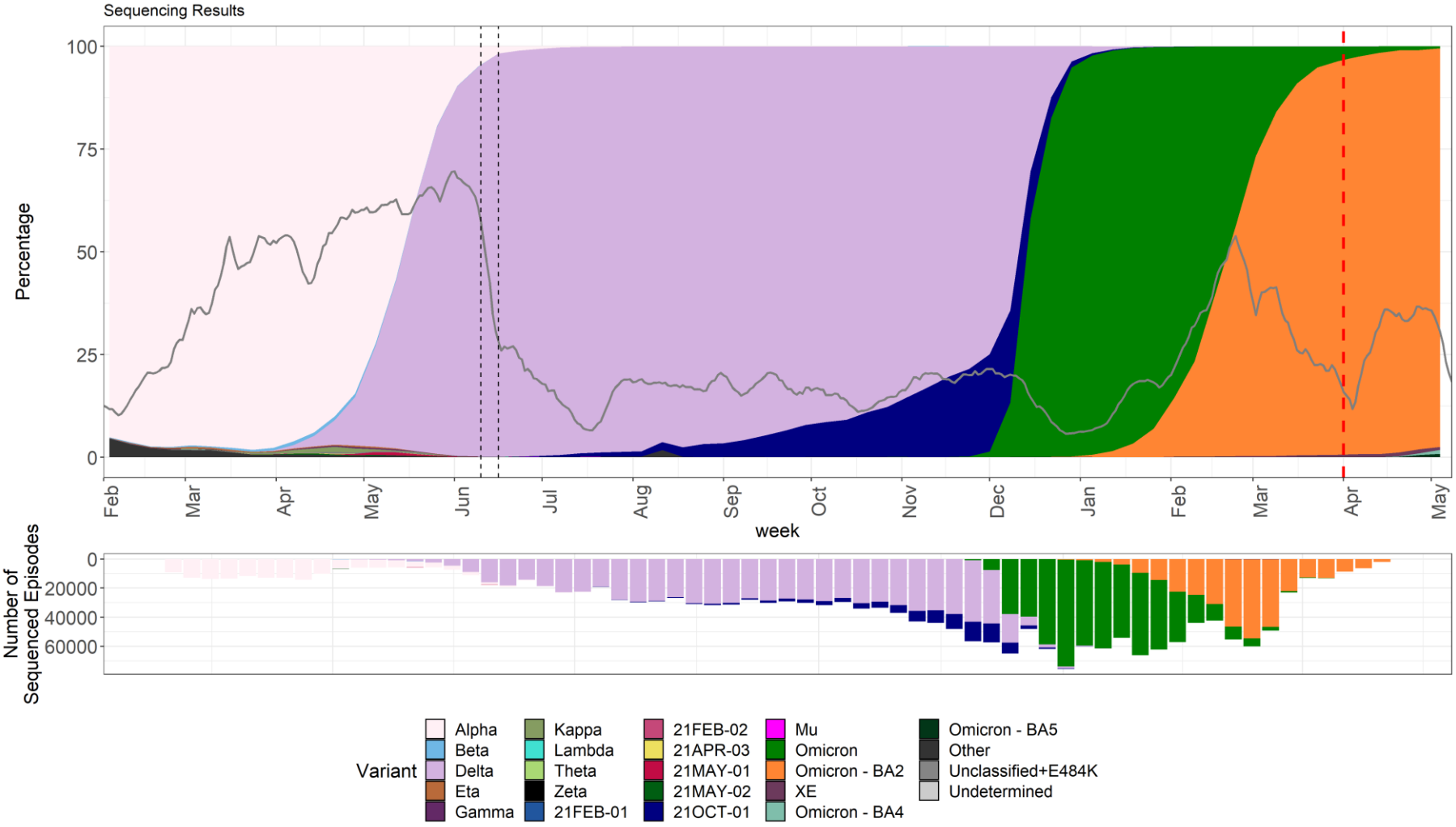
* Includes whole genome sequenced cases only

Find accessible data used in this graph in underlying data.

1.3 Variant prevalence

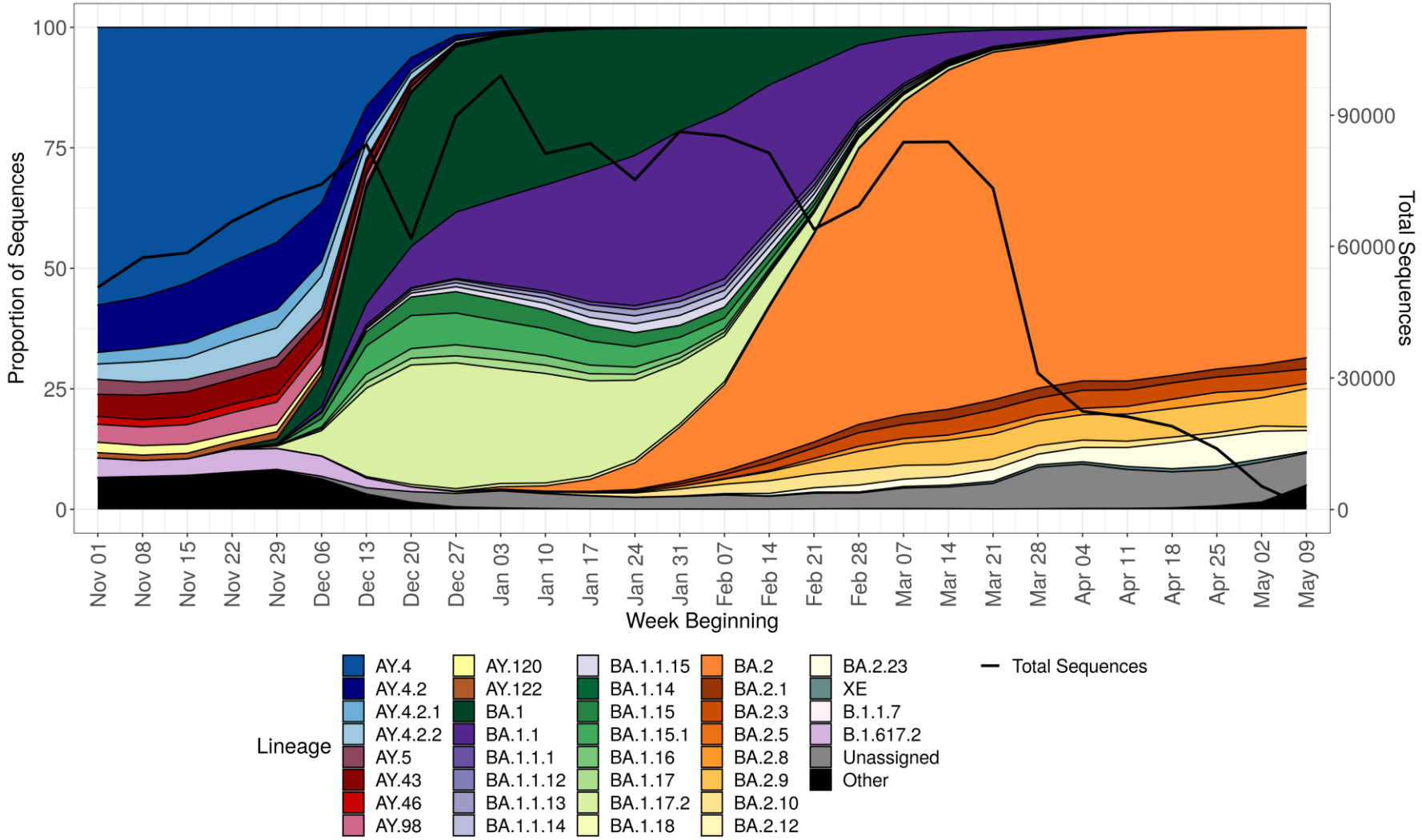
The prevalence of different UKHSA-designated variants amongst sequenced episodes is presented in Figure 5 and by Pangolin designation in Figure 6. Of the sequenced episodes from 24 April to 8 May 2022, 97.0% were Omicron lineage BA.2 (VOC-22JAN-01) and 0.4% were Omicron lineage BA.1 (VOC-21NOV-01). A further 2.6% were made up of Omicron lineage BA.4 (VOC-22APR-03), Omicron lineage BA.5 (VOC-22APR-04) and Omicron recombinant XE (V-22APR-02).

Figure 5. Variant prevalence of available sequenced episodes for England from 1 February 2021 as of 17 May 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 6. Prevalence of Pangolin lineages in the UK with sequence data from 1 November 2021 to 15 May 2022



The ‘Other’ category in Figure 6 includes genomes where the total number of genomes for that lineage and relevant sub-lineages is fewer than 5,000. The ‘Unassigned’ category includes genomes where the quality is insufficient to determine a lineage using Pangolin.

The total number of valid sequence results per week is shown by the black line. Only lineages with more than 5,000 sequences are shown. Smaller lineages are either merged with parent lineages (for example, AY.3.1 is included in AY.3) or are included in 'Other'. Sequences where Pangolin could not assign a lineage due to poor quality data are 'Unassigned' in this plot. Lineages XE, BA.4 and BA.5 are not currently at a high enough prevalence to meet the 5,000-sequence cut-off so are included in Other in this plot. Find accessible data used in this graph in underlying data.

1.4 Variant modelling

A logistic growth model is fitted to data from GISAID, to model:

- the fraction of sequenced cases that are BA.4 in South Africa (Western Cape), UK, USA and Denmark
- the fraction of sequenced cases that are BA.5 in Germany, Portugal, Denmark, France, UK and USA
- the past replacement of BA.1 lineages by BA.2 lineages in the countries listed above, to serve as a benchmark

Countries and regions were included based on having:

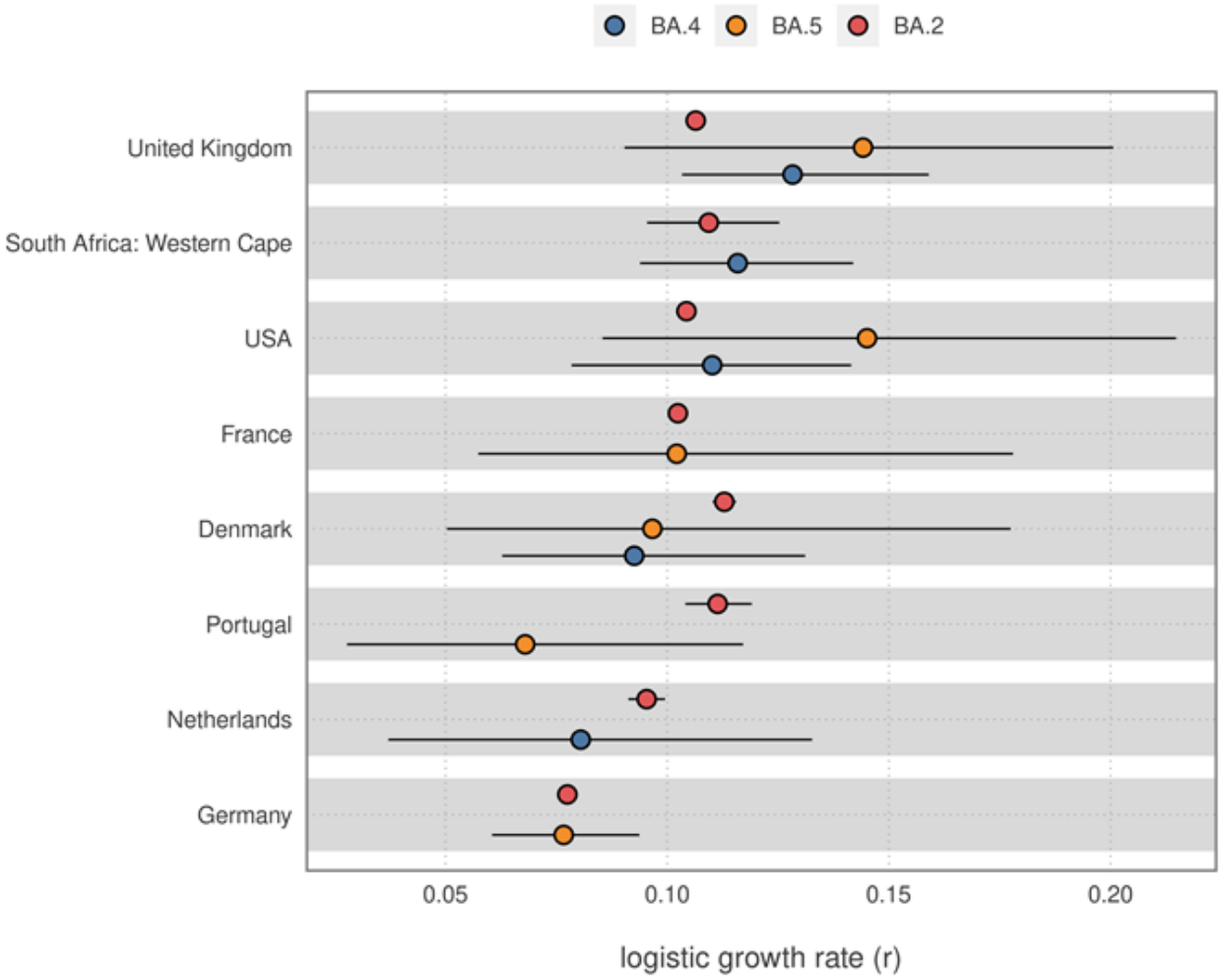
- detected BA.4 and BA.5 cases
- a share of sequenced BA.4 and BA.5 cases that broadly increased coherently day-on-day in a way that suggested the identification of cases from within-country transmission, not imported cases

Uncertainty is high (Figure 7), but in many countries the rate of replacement of BA.4 and BA.5 over BA.2 are comparable to the rate at which BA.2 replaced BA.1 (Figure 8), which could indicate a similar growth advantage. BA.5 appears to have a larger growth advantage than BA.4.

Table 2. Percentage of BA.4 and BA.5 samples by country

Date of estimate	Variant	Country	Percentage
08/05/2022	BA.4	Denmark	0.52% (CI: 0.25 to 1.05)
08/05/2022	BA.4	Netherlands	2.43% (CI: 0.94 to 5.95)
08/05/2022	BA.4	South Africa: Western Cape	77.72% (CI: 67.55 to 85.81)
08/05/2022	BA.4	UK	1.24% (CI: 0.77 to 2.05)
08/05/2022	BA.4	USA	0.77% (CI: 0.41 to 1.37)
08/05/2022	BA.5	Denmark	0.41% (CI: 0.16 to 0.96)
08/05/2022	BA.5	France	0.98% (CI: 0.24 to 5.11)
08/05/2022	BA.5	Germany	1.28% (CI: 0.9 to 1.79)
08/05/2022	BA.5	Portugal	18.47% (CI: 6.77 to 44.65)
08/05/2022	BA.5	UK	1.28% (CI: 0.61 to 2.52)
08/05/2022	BA.5	USA	0.78% (CI: 0.29 to 2.05)

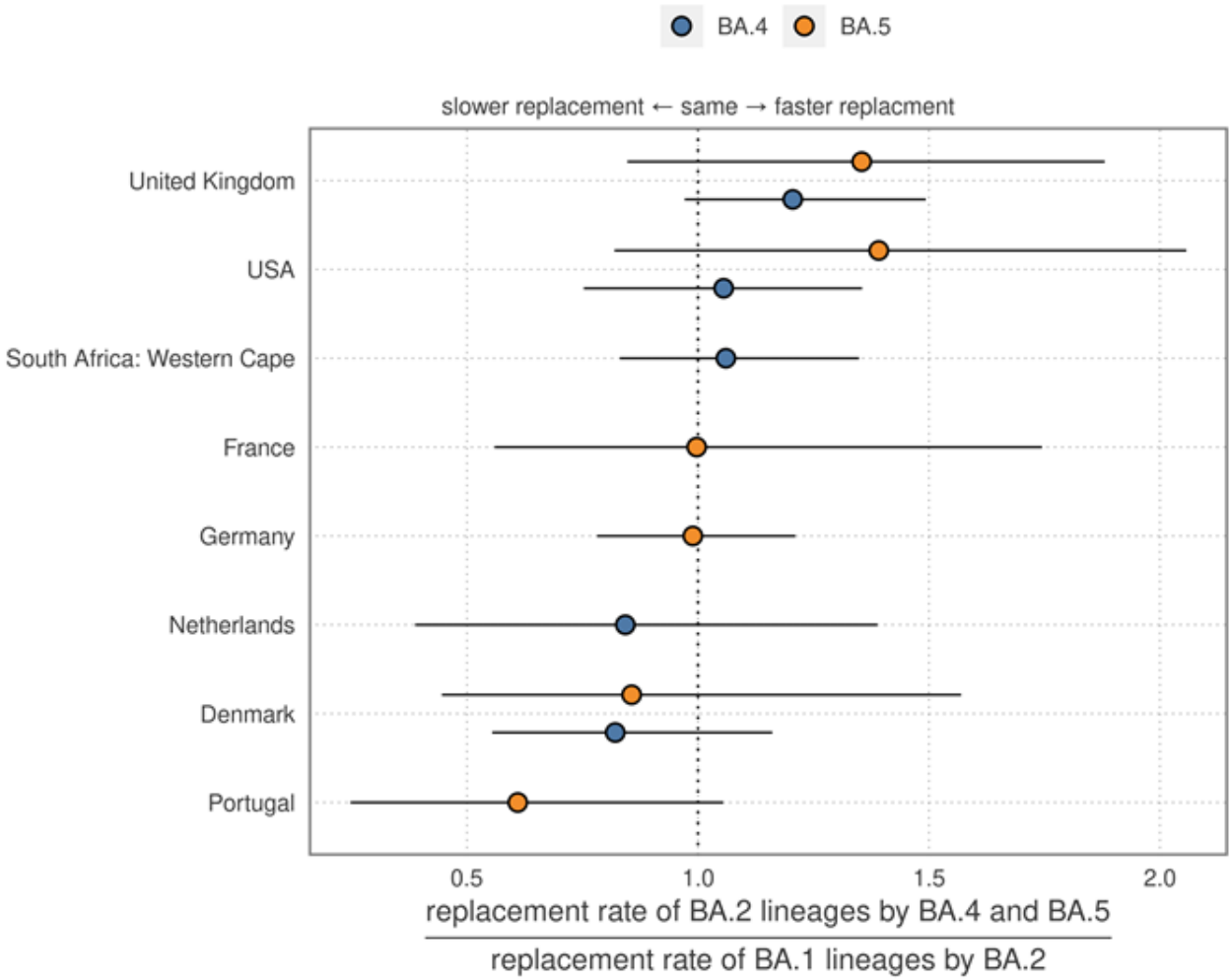
Figure 7. Logistic growth model to sequenced cases from GISAID



This figure describes changes in the representation of BA.4 and BA.5. As a comparison, we also model how quickly BA.2 replaced BA.1. The estimated logistic growth rate (x-axis) for each lineage is shown with 95% credible intervals. Note that due to sample size constraints not all variants were analysed for all countries. Supplementary data is not available for this figure.

The estimated growth rate for BA.4 and BA.5 replacing BA.2 is compared with the rate at which BA.2 replaced BA.1. The analysis is unable to entirely statistically differentiate the rates for the ongoing replacement of BA.2 by BA.4 and BA.5 as being faster or slower than the replacement of BA.1 by BA.2. In all countries, the credible intervals for the rate being faster / slower cross one (equivalence).

Figure 8. Logistic growth model to sequenced cases from GISAID



The logistic growth rates for BA.4 and BA.5 were divided by the estimate for BA.2. This gives the ratio of the growth rates. If this ratio is greater than one, then BA.4 and BA.5 are replacing BA.2 more quickly than BA.2 replaced BA.1. A ratio of one means the rates are equal, under one BA.4 and BA.5 are replacing BA.2 more slowly. We are unable to statistically differentiate the rates, though they look comparable overall. Supplementary data is not available for this figure.

Relative growth rates

The representation of different variants among sequenced cases is modelled in England for the last 3 months. Generalised additive models (GAMs) are fit with a negative binomial error structure to weekly-aggregated counts of variants to determine growth rates. An offset term is used to control for sampling effort. Models are fit at the weekly timescale due to small daily sample sizes. This means doubling times refer for the time for the weekly representation of variants to double or halve. Only variants that were sequenced 10 or more times in the past 2 weeks are included (Figure 9).

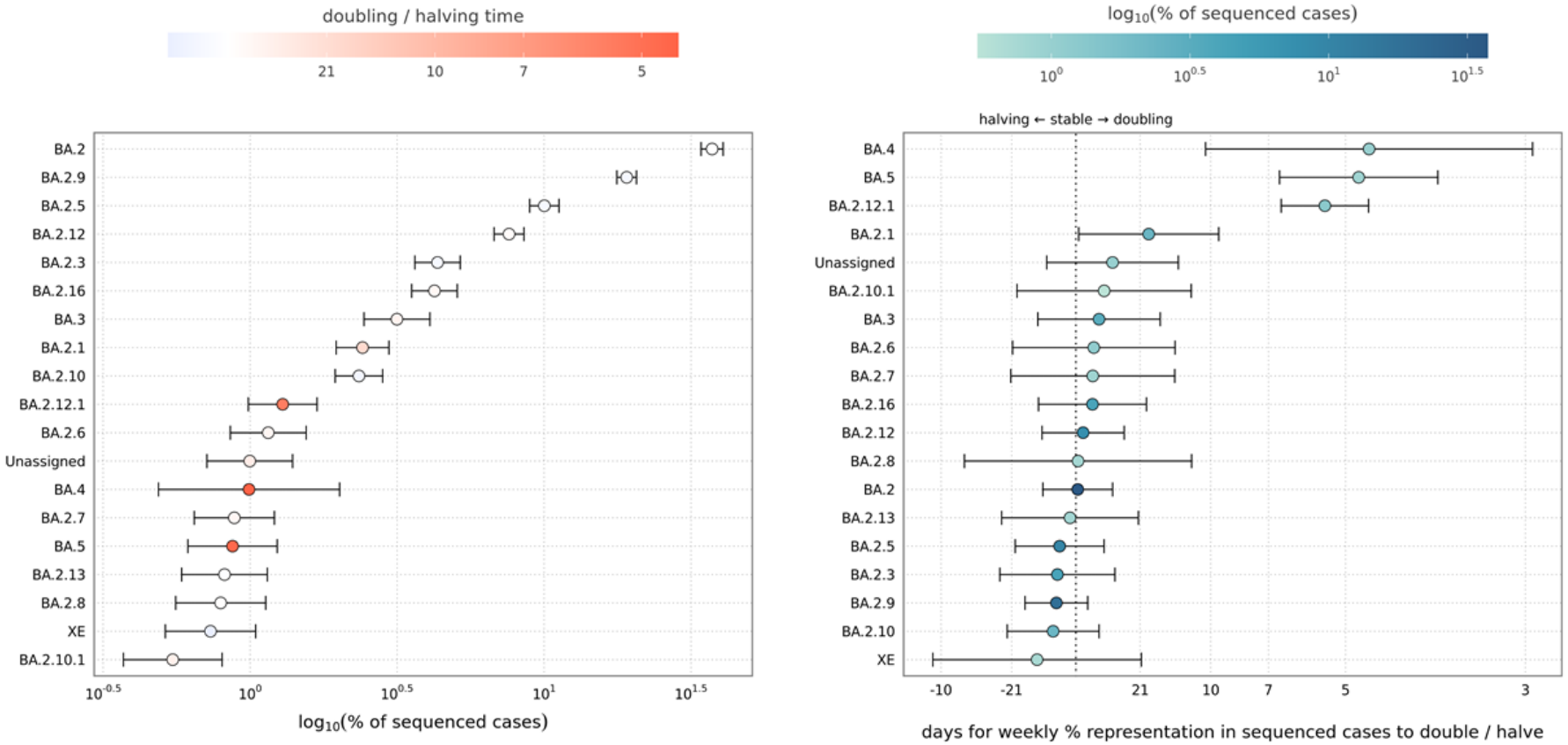
Variants of note are:

- BA.4 and BA.5 are driving a wave in South Africa – these variants can be identified through S-gene target failure
- XE, which is a recombinant that has been growing in the England for months
- BA.2.12.1, which is growing rapidly in the USA

Table 3. Sample counts by variant

Date of estimate	Variant	Total samples	Percentage	Doubling time
08/05/2022	XE	1274	0.73% (CI: 0.51 to 1.04)	-34.77 days (CI: -9.43 to 20.6)
08/05/2022	BA.2.12.1	96	1.29% (CI: 0.99 to 1.69)	5.42 days (CI: 6.57 to 4.61)
08/05/2022	BA.5	55	0.87% (CI: 0.61 to 1.24)	4.77 days (CI: 6.62 to 3.73)
08/05/2022	BA.4	68	0.99% (CI: 0.49 to 2.02)	4.6 days (CI: 10.4 to 2.95)

Figure 9. Representation and growth rate of sequenced cases in England



Only variants with 10 or more detections in the last 2 weeks were analysed. Generalised additive models were fitted 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 is not available for this figure.

Part 2. VOC-22APR-03 (BA.4)

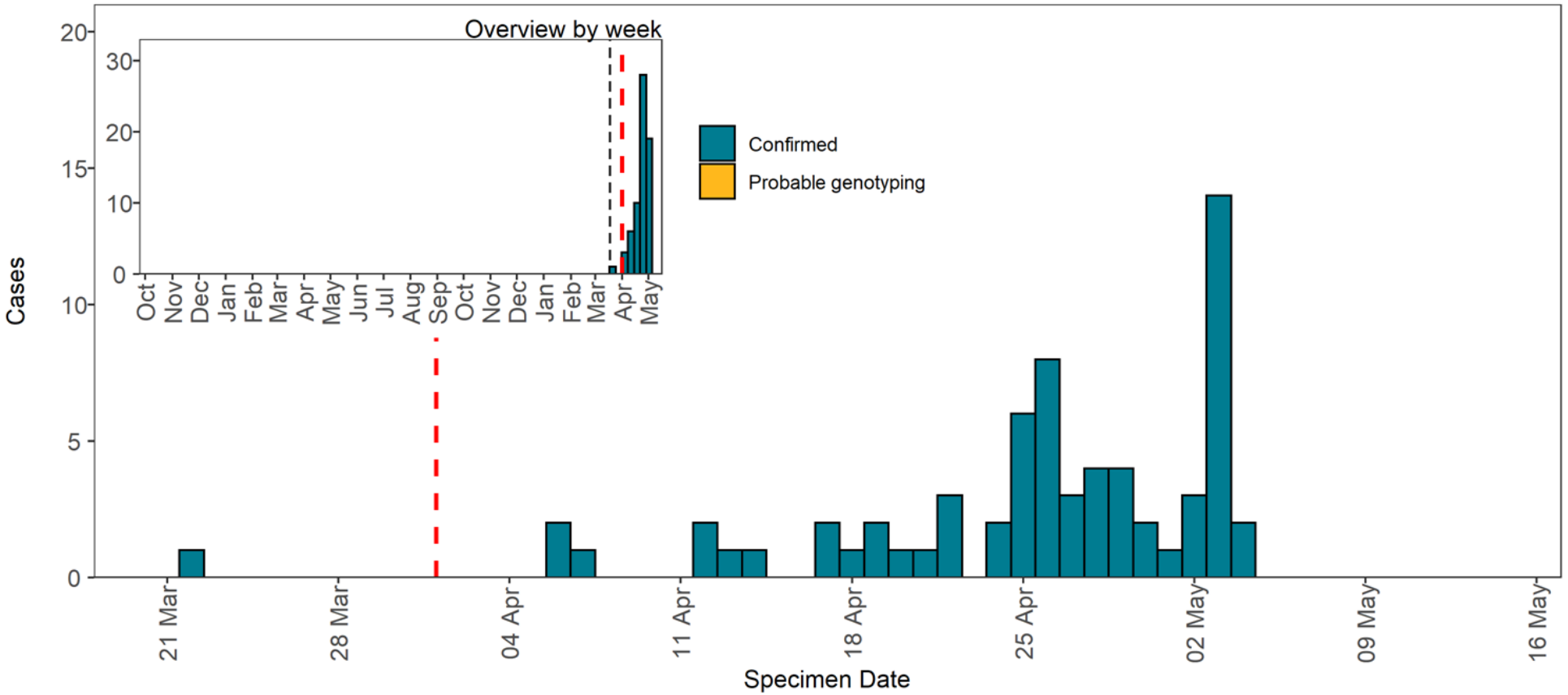
Omicron sub-lineage BA.4 was identified as part of horizon scanning on 4 April 2022. On 6 April 2022, the Variant Technical Group classified Omicron sub-lineage BA.4 as V-22APR-03. On 18 May 2022, UKHSA re-classified V-22APR-03 as VOC-22APR-03.

The revised genomic case definition for V-22APR-03 is available in Technical Briefing 41.

2.1 Epidemiology of VOC-22APR-03 (BA.4) in England

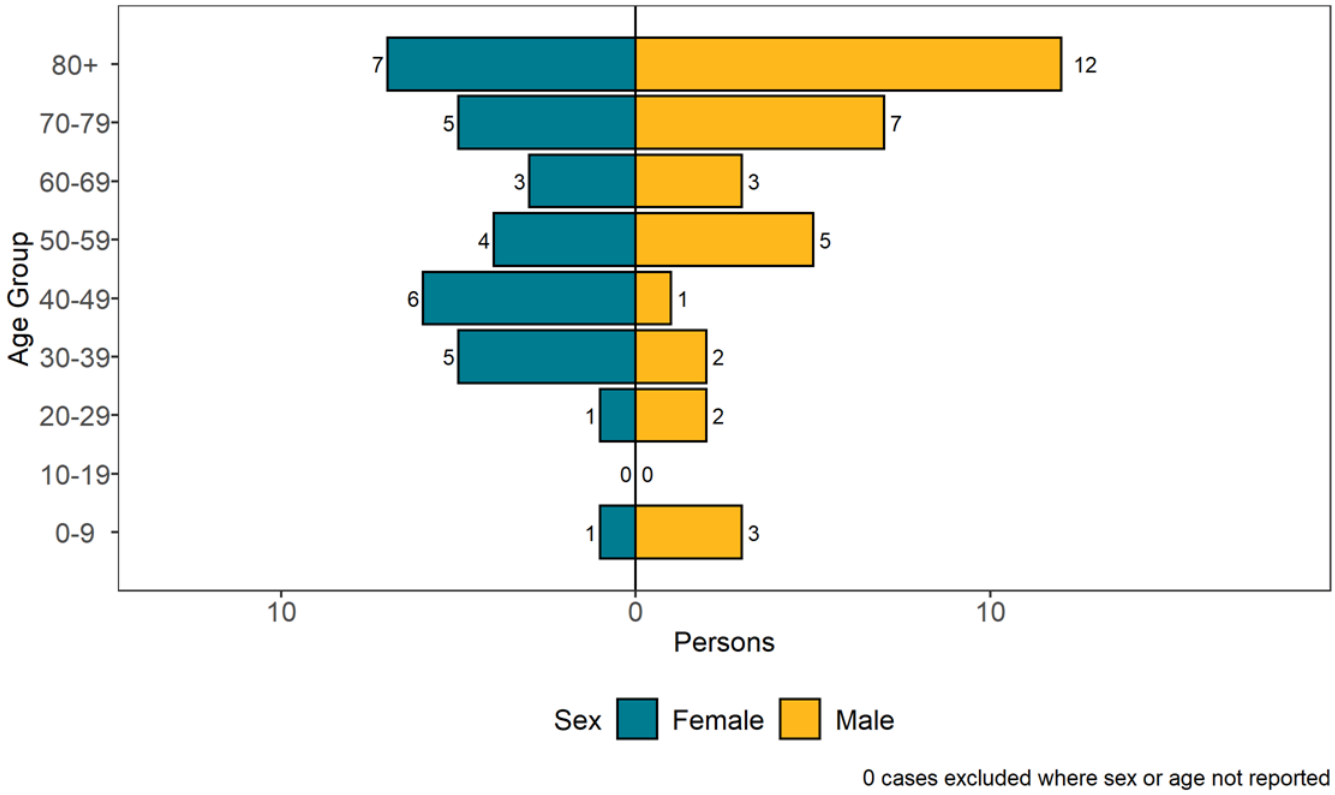
One hundred and fifty-six sequences assigned to the BA.4 in the UK genomics dataset up to 17 May 2022, of these 108 were associated with England, 104 of which were linked to patient information. Cases are increasing and geographically distributed across England with most cases in London, South East and West Midlands.

Figure 7. Confirmed (sequencing) and probable (genotyping) V-22APR-03 (BA.4) cases in England by specimen date and detection method as of 17 May 2022



Find accessible data used in this graph in underlying data.

Figure 8. Age-sex pyramid of V-22APR-03 cases as of 17 May 2022



Find accessible data used in this graph in underlying data.

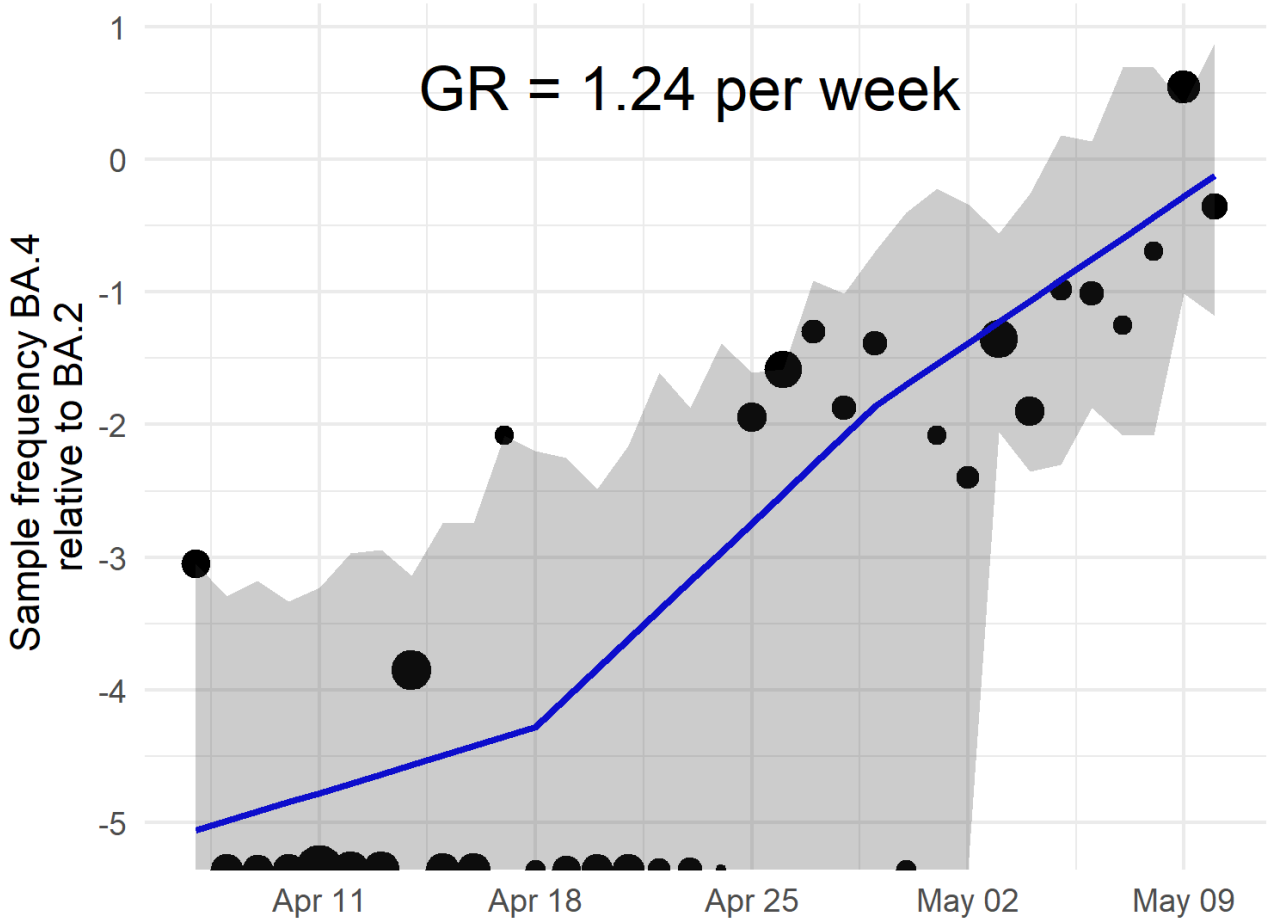
2.2 Growth rate

The growth rate of a novel variant is calculated relative to a matched control. Matched controls are samples of other circulating variants selected from the same time and location. For BA.4, genomes identified as BA.4 are compared to co-circulating BA.2 only. A statistical model was run to calculate the probability of a sampled genome being from the novel variant versus from the control over time. Growth rates are calculated per week or per day and are expressed on a log scale. A logistic growth rate of 0.5 per week indicates that the variant is increasing by a multiplicative factor of exp (0.5) =1.65 per week in comparison to the control. A logistic growth rate of zero would indicate no difference in growth rates between the 2 variants.

Using a control adjusts for geographic and temporal variation in case numbers, but despite these adjustments, differences in growth rates can be due to epidemiological factors such as founder effects and sampling, especially early on. Over time, the growth rate of a variant will converge towards an estimate of the variant's inherent transmissibility in comparison to other circulating variants. The growth rate is estimated by logistic regression of the number of genomes sampled with the BA.4 and BA.2 lineages on time of sample collection.

To adjust for geographic variation in case growth rates, BA.4 growth rates were estimated relative to a geographically matched sample of BA.2 genomes. Data sampled between 1 April 2022 and 11 May 2022 were included. The median growth rate is 124% per week (Figure 9). Patterns across regions are inconsistent and not reported.

Figure 9. Sample frequency of BA.4 (VOC-22APR-03) relative to Omicron (BA.2) over time



Supplementary data is not available for this figure.

2.3 International epidemiology

The earliest BA.4 sample in GISAID was from South Africa with a sample collection date of 10 January 2022. As of 16 May 2022, there were 1,385 GISAID sequences reported with this lineage from the following countries: South Africa (826), USA (124), United Kingdom (116), Austria (80), Denmark (47), Belgium (36), Germany (35), Israel (32), Italy (24), Australia (19), Netherlands (11), Spain (10), France (7), Canada (7), Singapore (3), Switzerland (3), Ireland (2), Botswana (1), New Zealand (1), and Chile (1). The increase in the number of genomes and geographic distribution suggests that the variant is transmitting successfully. Sampling strategies for many countries are unknown.

Part 3. Enhanced analyses of VOC-22APR-04 (BA.5)

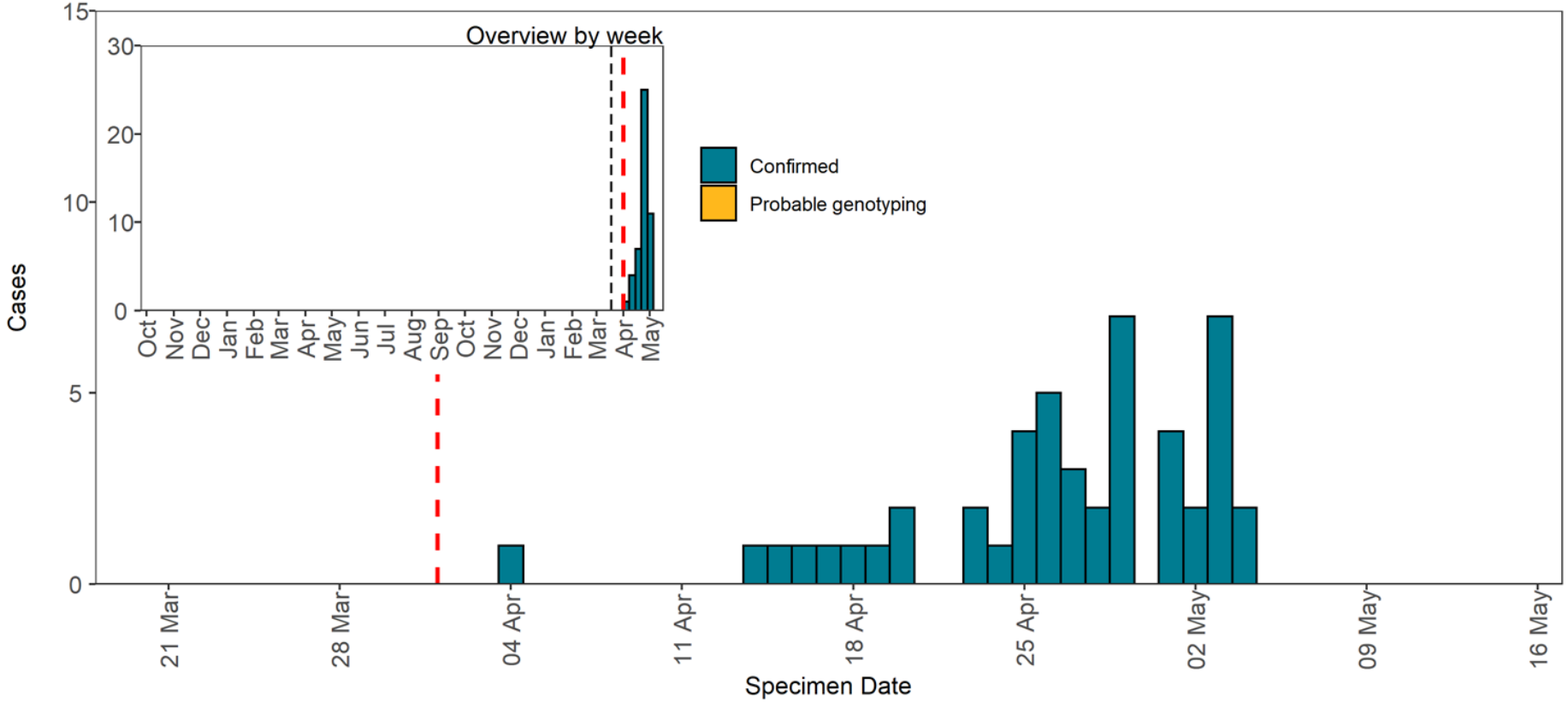
Omicron sub-lineage BA.5 was identified as part of horizon scanning on 4 April 2022. On 6 April 2022, the Variant Technical Group classified Omicron sub-lineage BA.5 as V-22APR-04. On 18 May 2022, UKHSA re-classified V-22APR-04 as VOC-22APR-04.

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

3.1 Epidemiology of VOC-22APR-04 (BA.5) in England

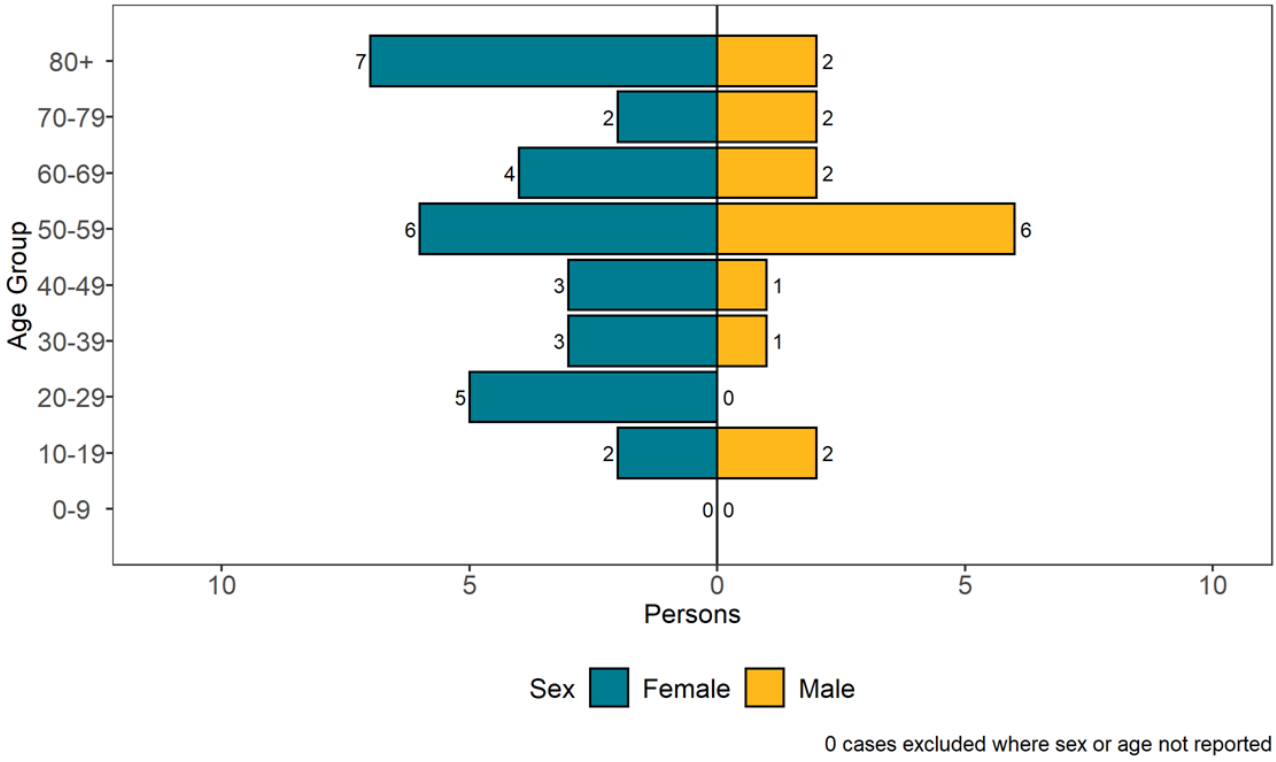
One hundred and nine sequences assigned to the BA.5 in the UK genomics dataset up to 17 May 2022, of these 74 were associated with England, 71 of which were linked to patient information. Cases are geographically distributed across England with most cases in the South East and South West.

Figure 10. Confirmed (sequencing) and probable (genotyping) V-22APR-04 (BA.5) cases in England by specimen date and detection method as of 17 May 2022



Find accessible data used in this graph in underlying data.

Figure 11. Age-sex pyramid of V-22APR-04 (BA.5) cases as of 17 May 2022



Find accessible data used in this graph in underlying data.

3.2 Growth rate

Growth rates for BA.5 are being closely monitored. Preliminary analyses demonstrate a growth advantage less extreme than for BA.4; however, as BA.5 sample numbers remain small (<100), this estimate in unstable.

3.3 International epidemiology

As of 16 May 2022, there were 809 GISAID sequences reported with this lineage from the following countries: South Africa (272), Germany (145), Portugal (133), United Kingdom (77), USA (58), Israel (20), Austria (19), Spain (19), Denmark (17), Netherlands (10), Belgium (9), France (9), Australia (6), Italy (5), Iceland (4), Switzerland (2), Hong Kong (2), Canada (1), and Norway (1). The increase in the number of genomes and geographic distribution suggests that the variant is transmitting successfully. This lineage shows sample dates between 5 January and 16 May 2022. Sampling strategies for many countries remain unknown.

Part 4. Updated epidemiology of XE (V-22APR-02)

XE is a BA.1 and BA.2 recombinant (containing BA.1 mutations for NSP1-6 and BA.2 mutations for the rest of the genome). It also has 3 mutations that are not present in all BA.1 or BA.2 sequences: NSP3 V1069I (non-synonymous) and C3241T (synonymous), and NSP12 C14599T (synonymous).

As of 17 May 2022, there are 2,049 XE sequences in the UK data with 1,569 XE cases in England. Cases are geographically distributed across England, with the first case detected via sequencing on 19 January 2022, and most cases in the East of England, London, and the South East. As of 17 May 2022, a total of 1,545 episodes of V-22APR-02 have been reported in England. XE remains at a low prevalence. Between 3 April 2022 and 17 May 2022, XE accounted for 0.7% of sequenced cases reported in England.

Part 5. Omicron VOC-22JAN-01 (BA.2)

The mutation profile of the Omicron sub-lineages was previously reported in Technical Briefing 31.

BA.2 has been reclassified as a VOC under the new classification on 1 April 2022.

5.1 Genomic diversity

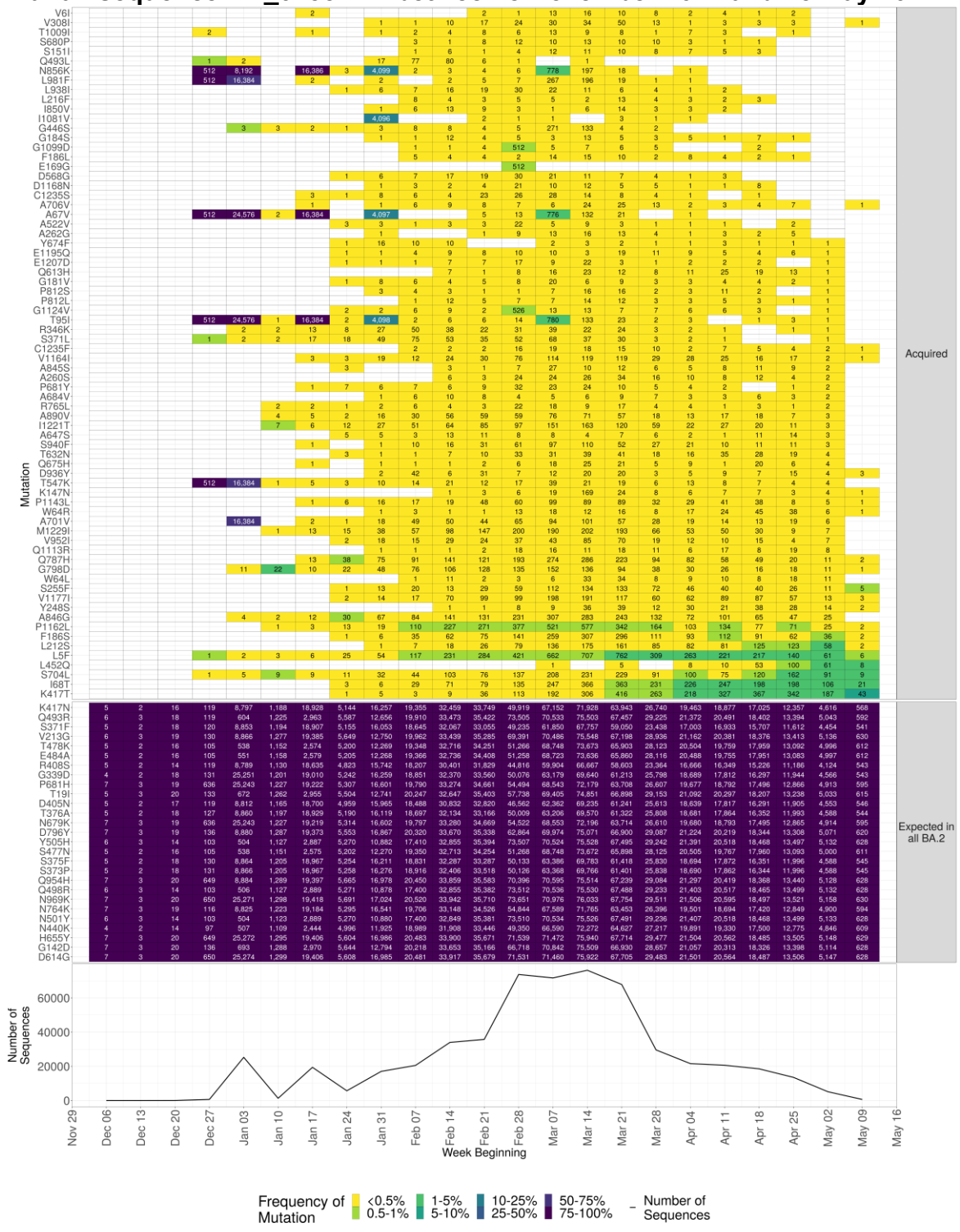
Diversity in Spike

Spike mutations are monitored within BA.2 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. Seventy-two additional mutations have been observed in BA.2 sequences according to the criteria in Table 2 (Figure 12). 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 12. Spike mutations found in BA.2 genomes in the UK dataset relative to the Wuhan sequence NC_045512.2 between 8 November 2021 and 15 May 2022

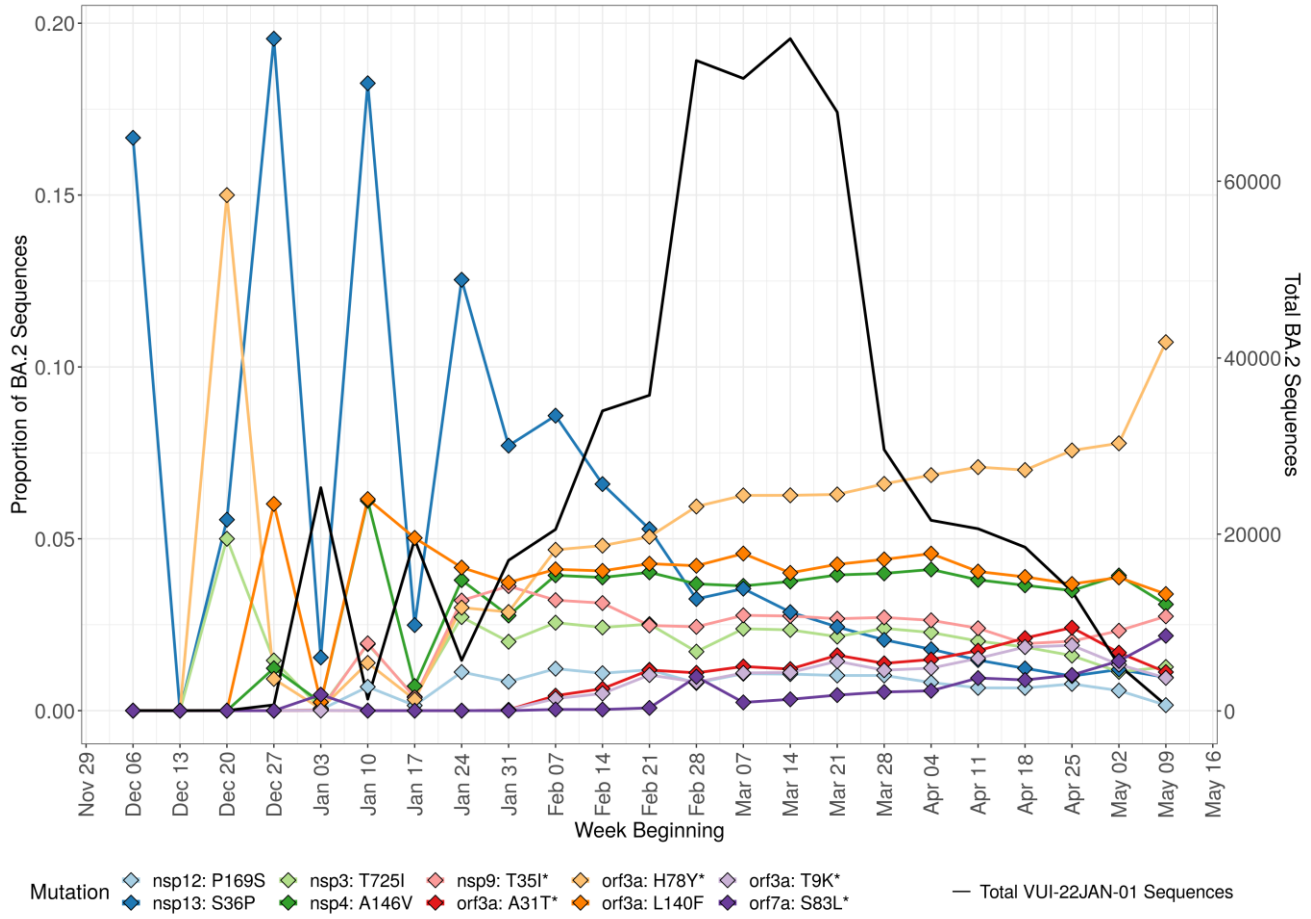


Find accessible data used in this graph in underlying data.

NB: all mutations in the sequence alignment are reported in these plots for review purposes.

Outside of Spike, there are 10 mutations that are present in at least 1% of BA.2 sequences for at least 3 consecutive weeks (Figure 13).

Figure 13. Mutations acquired by BA.2 outside of Spike, shown as a proportion of total BA.2 sequences (6 December 2021 and 15 May 2022)



The total number of BA.2 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.2 mutation set. Those that are considered additional, and that are present in at least 1% of BA.2 sequences for at least 3 consecutive weeks in the UK dataset, are included in Figure 13 as a proportion of total BA.2 sequences. Mutations labelled with * 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, the UKHSA Second Generation Surveillance System, the Secondary Uses Service data set, Emergency Care Data Set and the UKHSA Case and Incident Management System.

Authors of this report

UKHSA Genomics and Public Health Analysis Team

UKHSA Outbreak Surveillance Team

UKHSA COVID-19 Epidemiology Cell

UKHSA Immunisations Team

UKHSA Surveillance Team

UKHSA Public Health Incident Directors

UKHSA Data, Analytics and Surveillance

Contributions from the Variant Technical Group

Variant Technical Group members

Person	**Institution**
Meera Chand (Chair)	UKHSA
Genomics and bioinformatics	
Andrew Rambaut	University of Edinburgh
Thomas Peacock	UKHSA / Imperial College London
Matt Holden	Public Health Scotland
Nicholas Loman	UKHSA/University of Birmingham
Richard Myers	UKHSA
Anna Seale	UKHSA
Virology and Immunology	
Bassam Hallis	UKHSA

Person	Institution
Gavin Screaton	University of Oxford
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
Emma Thomson	University of Glasgow/London School of Hygiene and Tropical Medicine
Epidemiology and modelling	
Charlotte Anderson	UKHSA
Chris Williams	Public Health Wales
Daniela de Angelis	University of Cambridge
Erik Volz	Imperial College London
Jamie Lopez-Bernal	UKHSA
John Edmunds	London School of Hygiene and Tropical Medicine
Julia Gog	Scientific Pandemic Influenza Group on Modelling / University of Cambridge
Maria Rossi	Public Health Scotland
Neil Ferguson	Imperial College London
Richard Elson	UKHSA
Simon Thelwall	UKHSA
Susan Hopkins	UKHSA
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

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