UK Health Security Agency

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

## Technical briefing 26

22 October 2021

This briefing provides an update on previous briefings up to 15 October 2021

# Contents

# Summary

This extra report has been produced to provide information on the new Variant Under Investigation VUI-21OCT-01, AY.4.2.

The specialist technical briefings contain early data and analysis on emerging variants and findings have a high level of uncertainty.

In summary:

1. AY.4.2. accounts for a slowly increasing proportion of cases in the UK. It is also present in multiple other countries on GISAID and is seen in travellers to the UK from a large number of countries. It is not clear where it originated or when.

2. This lineage has the mutations of Delta and AY.4, and in addition S: A222V and Y145H. These mutations are in the N terminal domain. They could plausibly be biologically significant but there is minimal laboratory evidence.

3. AY.4.2. appears to have a modestly increased growth rate compared to Delta. Growth rates are included here and similar findings were reported by another Variant Technical Group contributor using a different method. A high observed growth rate may be due to a biological change in the virus (transmissibility or immune escape) or to epidemiological context, such as being introduced into an area or population subgroup with high existing levels of transmission. It is still uncertain whether AY.4.2 is growing due to a biological difference.

4. The secondary attack rate for household contacts of cases with VUI-21OCT-01 was 12.4% (95% CI: 11.9% to 13.0%), higher than that observed for other Delta cases where it was 11.1% (95% CI: 11.0% to 11.2%). In non-household settings, the secondary attack rate was higher for VUI-21OCT-01 than other Delta cases, but this difference was not significant. No significant variation between regions was observed.

5. Based on these considerations and the high level of uncertainty, AY.4.2 was designated a new Variant Under Investigation, VUI-21OCT-01.

6. Preliminary epidemiology and some of the supporting data used in the VUI assessment are included in this report. In addition, comparative analyses of deaths, hospitalisation, and vaccine effectiveness have commenced and will be reported once available. Crude data on deaths and hospitalisations are included in this report for information but are not definitive analyses. Further severity and transmissibility modelling will be undertaken. Pseudovirus work has been initiated and residual biological materials are being cultured for live virus.

7. Lambda (C.37) and C36.3 have been de-escalated as of the 20 October 2021 to variants in monitoring.

All risk assessments are published separately, except for Gamma, which was published within Technical Briefing 7 and Alpha within Technical Briefing 9. As Delta is the dominant variant in the UK, epidemiological data in the weekly surveillance report is also relevant.

# Published information on variants

The collection page gives content on variants, including prior technical briefings. Definitions for variants of concern, variants under investigation, and signals in monitoring are detailed in Technical Briefing 8. Data on variants not detailed here is published in the Variant Data Update. Variant risk assessments are available in prior technical briefings.

Public Health England (PHE) (now UKHSA) curated a repository on the 5 March 2021 containing the up-to-date genomic definitions for all VOCs and VUIs. The repository is accessible on GitHub.

World Health Organization (WHO) nomenclature from 31 May 2021 is incorporated. A table incorporating WHO and UK designations with Pango lineages is provided below (Table 1). Following the table, variants are referred to using their WHO designation where this exists and the UK designation where it does not.

Technical briefings are published periodically. From technical briefing 15, briefings include variant diagnoses identified by whole-genome sequencing and a genotyping PCR test, including the categorisation of sequenced and genotyped variant results and a rules-based decision algorithm (RBDA) to identify variant and mutation (VAM) profiles from genotype assay mutation profiles. Genotyping is used to identify variants Alpha, Beta (or B.1.621), Delta, and Gamma. Targets were updated in mid-May 2021 to prioritise accurate identification of Delta over Alpha.

# Part 1. Surveillance overview

## 1.1 Variants under surveillance

Table 1 and Table 2 show the current VOC, VUI, and variants in monitoring detected and not detected in the UK as of 21 October 2021.

**Table 1. SARS-CoV-2 variants of public health interest: variants detected in the UK**

| WHO nomenclature | Lineage | Designation | Status |
|---|---|---|---|
| Alpha | B.1.1.7 | VOC-20DEC-01 | VOC |
| Beta | B.1.351 | VOC-20DEC-02 | VOC |
| Gamma | P.1 | VOC-21JAN-02 | VOC |
| Delta | B.1.617.2, AY.1, AY.2, AY.3, AY.33, AY.34 | VOC-21APR-02 | VOC |
| Delta | AY.4.2 | VUI-21OCT-01 | VUI |
| Eta | B.1.525 | VUI-21FEB-03 | VUI |
| | B.1.1.318 | VUI-21FEB-04 | VUI |
| Kappa | B.1.617.1 | VUI-21APR-01 | VUI |
| Mu | B.1.621 | VUI-21JUL-01 | VUI |
| | C.36.3 | VUI-21MAY-02 | De-escalated to monitoring |
| Epsilon^ | B.1.427/B.1.429 | | Monitoring |
| | B.1.620 | | Monitoring |
| | R.1 | | Monitoring |
| | C.1.2 | | Monitoring |

**Table 2. SARS-CoV-2 variants of public health interest: variants present in GISAID but not detected in the UK**

| WHO nomenclature | Lineage | Designation | Status |
|---|---|---|---|
| Theta^ | P.3 | VUI-21MAR-02 | VUI |
| | B.1.617.3 | VUI-21APR-03 | VUI |
| | AV.1 | VUI-21MAY-01 | VUI |
| Zeta | P.2 | VUI-21JAN-01 | VUI |
| Lambda | C.37 | VUI-21JUN-01 | De-escalated to Monitoring |
| | A.27 | | Monitoring |
| Iota | B.1.526 | | Monitoring |
| | B.1.1.7 with Q677H | | Monitoring |
| | B.1 with 214insQAS | | Monitoring |
| | AT.1 | | Monitoring |
| | B.1.629 | | Monitoring |
| | B.1.619 | | Monitoring |
| | B.1.630, B.1.631/B.1.628 | | Monitoring |
| | P.1.8 | | Monitoring |
| | P.5 | | Monitoring |

Provisionally extinct variants are excluded from these tables.

VOCs and VUIs 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 VUI has not been observed in the UK or international datasets within the preceding 12 weeks, it is designated as provisionally extinct, but monitoring remains in place.

## Changes to designations

On the 20 October 2021 Lambda was moved to a signal in monitoring, on the basis that it is being outcompeted by Delta, is no longer regularly seen in the UK and that there is only a modest reduction in neutralisation.

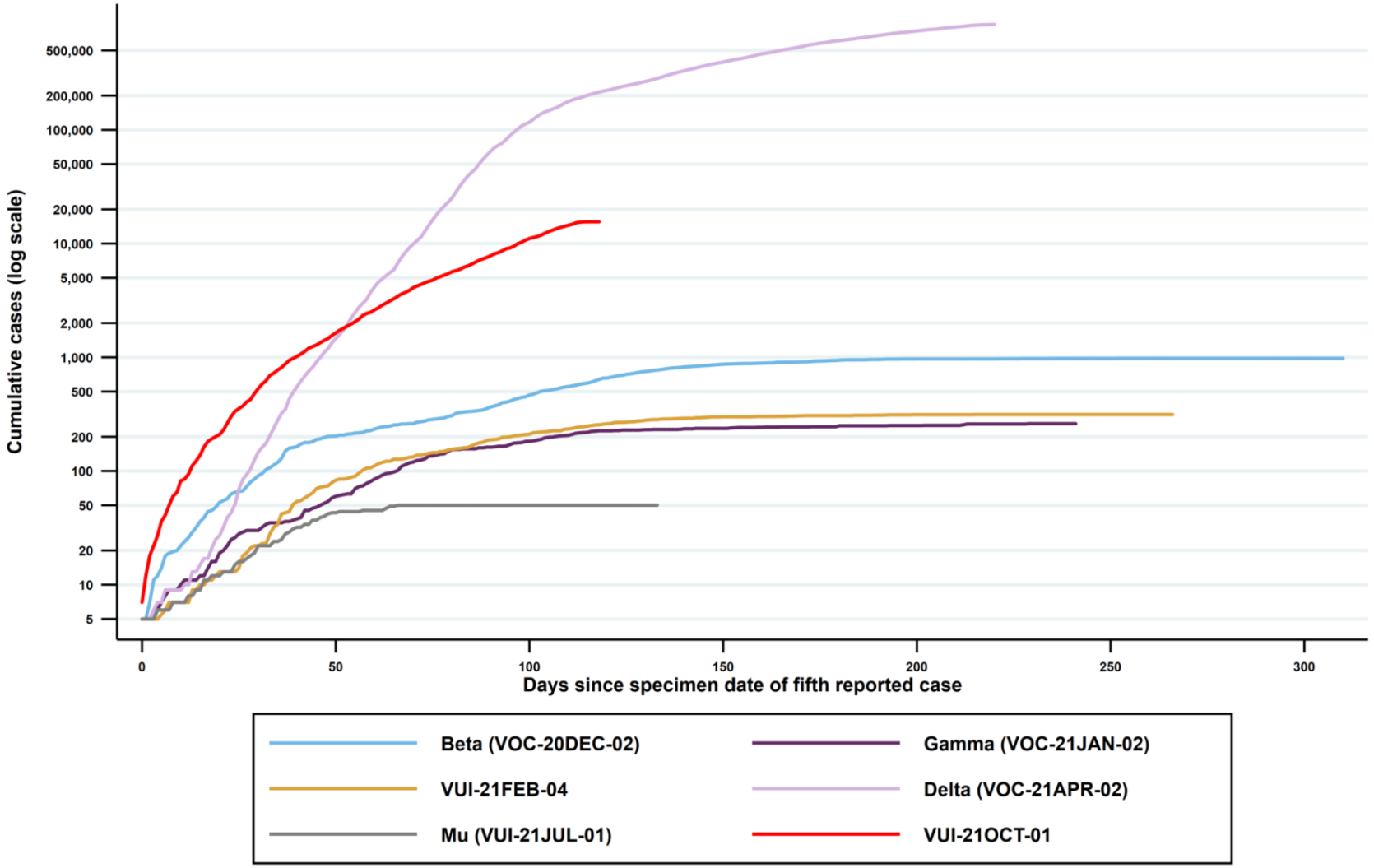
On the 20 October 2021 C36.3 was moved to a signal in monitoring, on the basis that it is no longer seen in the UK, has declined in all countries where it was present and has negligible reduction in neutralisation in comparison to Alpha/Delta.

The last documented UK cases of VUI-21JAN-01 was on 14 April 2021, VUI-21APR-03 on 17 May 2021, VUI-21MAR-02 on 25 May 2021, VUI-21MAY-01 on 21 June 2021 and are in International monitoring. Following the prior technical briefing VUI-21JUN-01 has been moved to international monitoring with the last documented case on 10 July 2021.

^ Zeta and Theta were de-escalated by WHO and are no longer WHO variants under monitoring. Kappa, Iota, Eta and Epsilon were de-escalated by WHO to WHO variants under monitoring.

Cumulative case numbers indicate VUI-21OCT-01 is increasing as shown in Figure 1.

**Figure 1. Cumulative cases in England of variants indexed by days since the fifth reported case as of 21 October 2021**



# Part 2. Enhanced analysis on specific variants. Delta VUI-21OCT-01 (AY.4.2)

The lineage B.1.617.2 was escalated to a variant of concern in the UK on 6 May 2021 (VOC-21APR-02). This variant was named Delta by WHO on 31 May 2021.

New sub-lineages of Delta are regularly identified and designated. The Delta sublineage AY.4.2 was designated VUI-21OCT-01 on 20 October 2021.

## 2.1 Surveillance case definitions

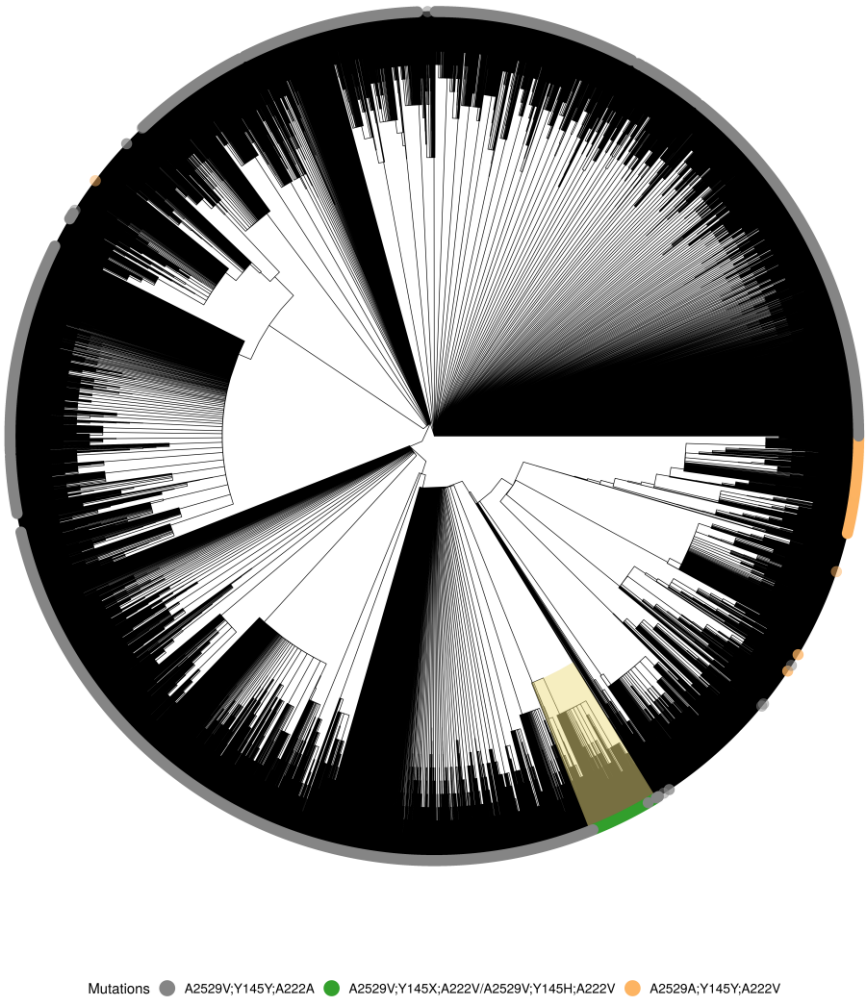
AY.4.2 includes the spike mutations A222V and Y145H, as well as the mutations seen in Delta and the AY.4 lineage. Y145H is in an area of the genome which has lower sequencing coverage with some primer sets. A222V is present in other clades outside AY.4.2.
To validate an approach for surveillance, a phylogenetic evaluation of potential SNP-based genomics case definitions has been undertaken. Within a sub-sampled UK tree of Delta sequences (n=115,097, Figure 2), the phylogenetic clade comprising the majority of the sequences with all 3 mutations was determined to correspond to the AY.4.2 lineage (Figure 2, highlighted clade).

The amino acid frequencies (and their combinations) at positions 222 and 145 in Spike, and 2529 in orf1ab (wild-type, mutant, or unknown) were generated to find the combinations that would best distinguish between AY.4.2 and non-AY.4.2.

Based on this analysis, the optimal surveillance case definition is a genome meeting the existing Delta genome case definition plus any 2 of the 3 mutations (orf1ab: A2529V; S: Y145H; S: A222V) where none of the positions are wild-type. This definition is highly specific (>99.9%) and sensitive (91.6%) for the clade in question. Figure 3 shows the clade and the mutation combinations seen in the sequences within it.

AY.4.2 can also be called by the latest version of Pangolin. The calling when assessed against the phylogenetic clade is slightly less (99.8%) specific at present. In the subsampled phylogeny (n=115,097), our conservative definition identified 2 sequences outside the clade to be AY.4.2 whereas Pangolin called 247. All variants have these issues with case definitions, but it is more pronounced amongst Delta sub-lineages because they differ by only a few mutations. Both Pangolin and SNP based definitions will be used in analysis; conservative SNP-based definitions will be used for surveillance. Definitions will be monitored for accuracy over time.

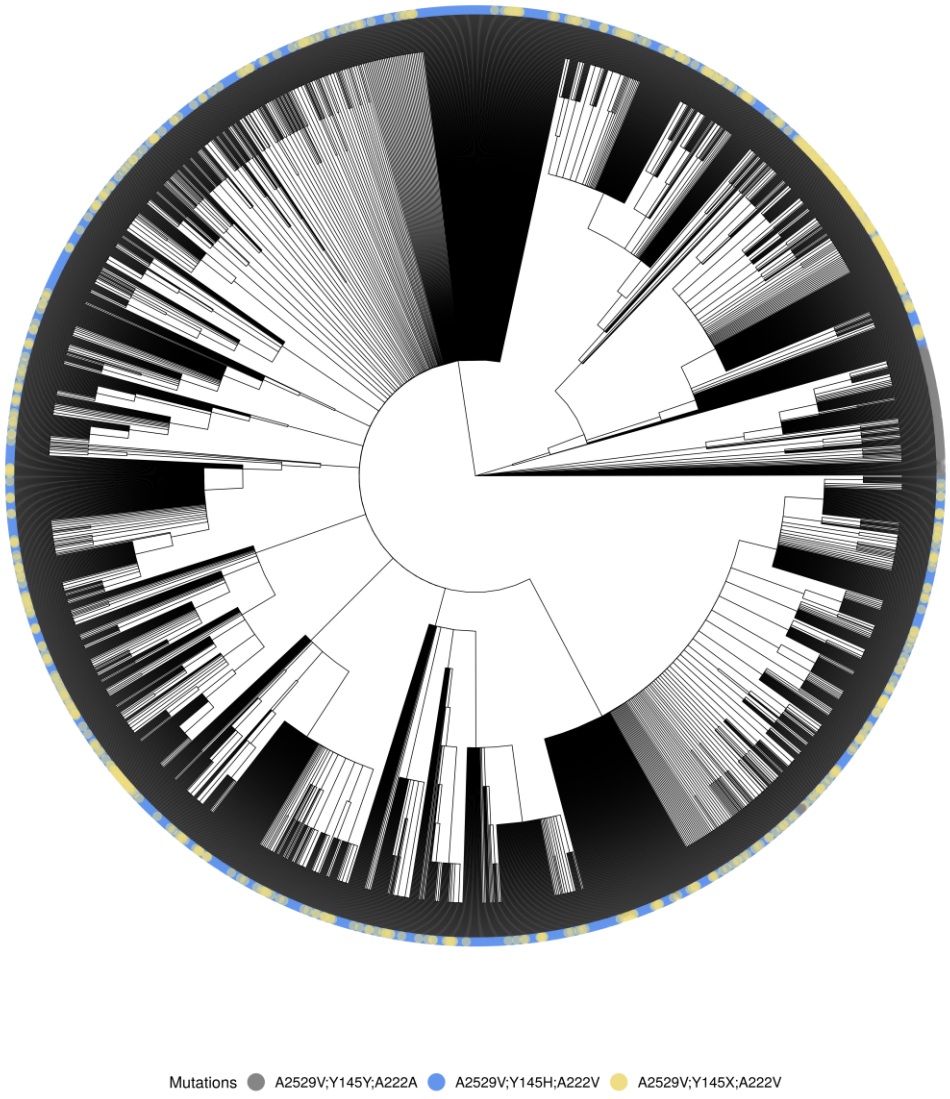
**Figure 2. Maximum likelihood sub-sampled phylogenetic tree of Delta variants from the UK with key mutations (A222V, Y145H and A2529V) highlighted, including VUI-21OCT-01 AY4.2 sub-lineage**




Supplementary data is not available for this figure.

This tree was built using Fasttree and Usher with a sub-sample of n=115,097 Delta sequences with image edge coloured by key mutations. To generate the sub-sample, Delta sequences were grouped by Pangolin lineage and week of sample. Where the group was 4 or more sequences, 25% of the group was selected at random to be included, where the group was smaller than 4 sequences, the whole group was included. Grey indicates sequences that have only the 2529V mutation, orange indicates sequences that have only the 222V mutation, green indicates sequences that meet the VUI-21OCT-01 definition (highlighted yellow clade). These sequences either contain all 3 mutations A222V, Y145H and A2529V) or have the 2529V and 222V mutations but the amino acid at site 145 could not be read (see Figure 3). Sequences with no coloured edge were an alternative mutation combination. Most of these are wild-type (222A, 145Y, 2529A) at all 3 positions.

**Figure 3. Extract of maximum likelihood phylogenetic sub-sampled tree of Delta variants from the UK of clade containing VUI-21OCT-01**




Supplementary data is not available for this figure.

The tree shows the highlighted clade from Figure 2. Yellow indicates sequences containing 2529V and 222V but where the amino acid at position 145 could not be determined. Blue indicates sequences containing all 3 mutations (A2529V, Y145H, A222V). Grey indicates sequences with 2529V but wildtype calls at 145 and 222.

# 2.2 Epidemiology of VUI-21OCT-21 in England

As of 21 October 2021, there are 22,017 VOC-21OCT-01 genomes in the UK dataset, linked to 15,120 cases in England. VUI-21OCT-01 accounts for 3.8%, 5.2%, and 5.9% of Delta cases in England in the weeks beginning 19 September, 26 September, and 3 October 2021 respectively (Figure 4). Data are incomplete for more recent weeks.

Variant prevalence for all cases in England as of 21 October 2021 is shown in Figure 4, by region in Figure 5 and travel status in Figure 6. Figure 7 shows AY.4.2 as a proportion of all Delta cases in England using Pangolin lineage call.

Cases have been detected across all regions in England (Table 5 and Figure 8). Of the 15,120, 420 had a recent travel history, with the most frequent country of travel being or Spain (96) or Greece (75). At least 32 countries of travel have been reported.
Age data are shown in Figure 9.

## Severity outcomes

To assess severe outcomes from VUI-21OCT-01 outcomes of cases between 15 May 2021 and 23 September 2021 were assessed and compared against Delta cases from the same time period. This time period was selected to cover the emergence of VUI-21OCT-01 and allow 28 days since first specimen to elapse to assess outcomes.

Information on attendance to emergency care is derived from the Emergency Care Data Set (ECDS) and Secondary Uses Service (SUS), provided by NHS Digital. These data only show whether a case has attended emergency care at an NHS hospital and was subsequently admitted as an inpatient. The data does not include cases who were directly admitted without first presenting to emergency care.

ECDS and SUS reporting is lagged, where NHS trusts routinely provide monthly data by the 21st of the following month. However, some trusts report daily data, and the linkage between coronavirus (COVID-19) cases and ECDS data is updated twice-weekly.

These initial crude analyses do not show strong evidence of a difference in risk of hospitalisation or death between VUI-21OCT-01 and Delta. However, these analyses do not adjust for crucial factors that can influence outcomes such as age and vaccination status and should be interpreted with caution.

**Table 3. Attendance to emergency care and inpatient admission of cases in England (15 May 2021 to 20 October 2021)**

| Variant | Number of cases since 15 May 2021[#] | Cases with an A&E visit or where presentation to A&E resulted in inpatient admission*(exclusion[‡]) | |
|---|---|---|---|
| | n | n | % |
| Delta | 704,541 | 1,739 | 0.25% (95% CI 0.24-0.26) |
| VUI-21OCT-01 | 8,666 | 27 | 0.31% (95% CI 0.21-0.45) |
| Total | 713,207 | 1,766 | 0.25% (95% CI 0.24-0.26) |

Data sources: Emergency care attendance and admissions from ECDS and SUS. NHS trusts are required to submit emergency care attendances by the 21st of each month. As a result, the number of cases with attendances may show substantial increases in technical briefs prepared after the monthly cut-off, compared with other briefs from the same month.
¥ Cases without specimen dates and unlinked sequences (sequenced samples that could not be matched to individuals) are excluded from this table.
* Cases are assessed for any emergency care attendance within 14 days of their positive specimen date.
# Inclusion: Including cases where 28 days has elapsed since their positive specimen date
‡ Exclusion: Excluding cases with the same specimen and attendance dates. Cases where specimen date is the same as date of emergency care visit are excluded to help remove cases picked up via routine testing in healthcare settings whose primary cause of attendance is not COVID-19. This underestimates the number of individuals in hospital with COVID-19 but only includes those who tested positive prior to the day of their emergency care visit. Some of the cases detected on the day of admission may have attended for a diagnosis unrelated to COVID-19.

**Table 4. Deaths of cases in England (15 May 2021 to 20 October 2021)**

| Variant | Number of cases since 15 May# (Exclusion‡) | Deaths^ | |
|---|---|---|---|
| | n | n | % |
| Delta | 704,440 | 3,813 | 0.54% (95% CI 0.52-0.56) |
| VUI-21OCT-01 | 8,665 | 62 | 0.72% (95% CI 0.55-0.92) |
| Total | 713,105 | 3,875 | 0.54% (95% CI 0.53-0.56) |

Data sources: deaths from PHE daily death data series (deaths within 28 days).
¥ Cases without specimen dates and unlinked sequences (sequenced samples that could not be matched to individuals) are excluded from this table.
# Inclusion: Including cases where 28 days has elapsed since their positive specimen date.
‡ Exclusion: Excluding cases who tested positive at post-mortem.
^ Total deaths in any setting (regardless of hospitalisation status) within 28 days of positive specimen date.

**Figure 4. Variant prevalence plot (all cases in England, genomic surveillance case definitions) as of 21 October 2021.**
(Find accessible data used in this graph in underlying data.)

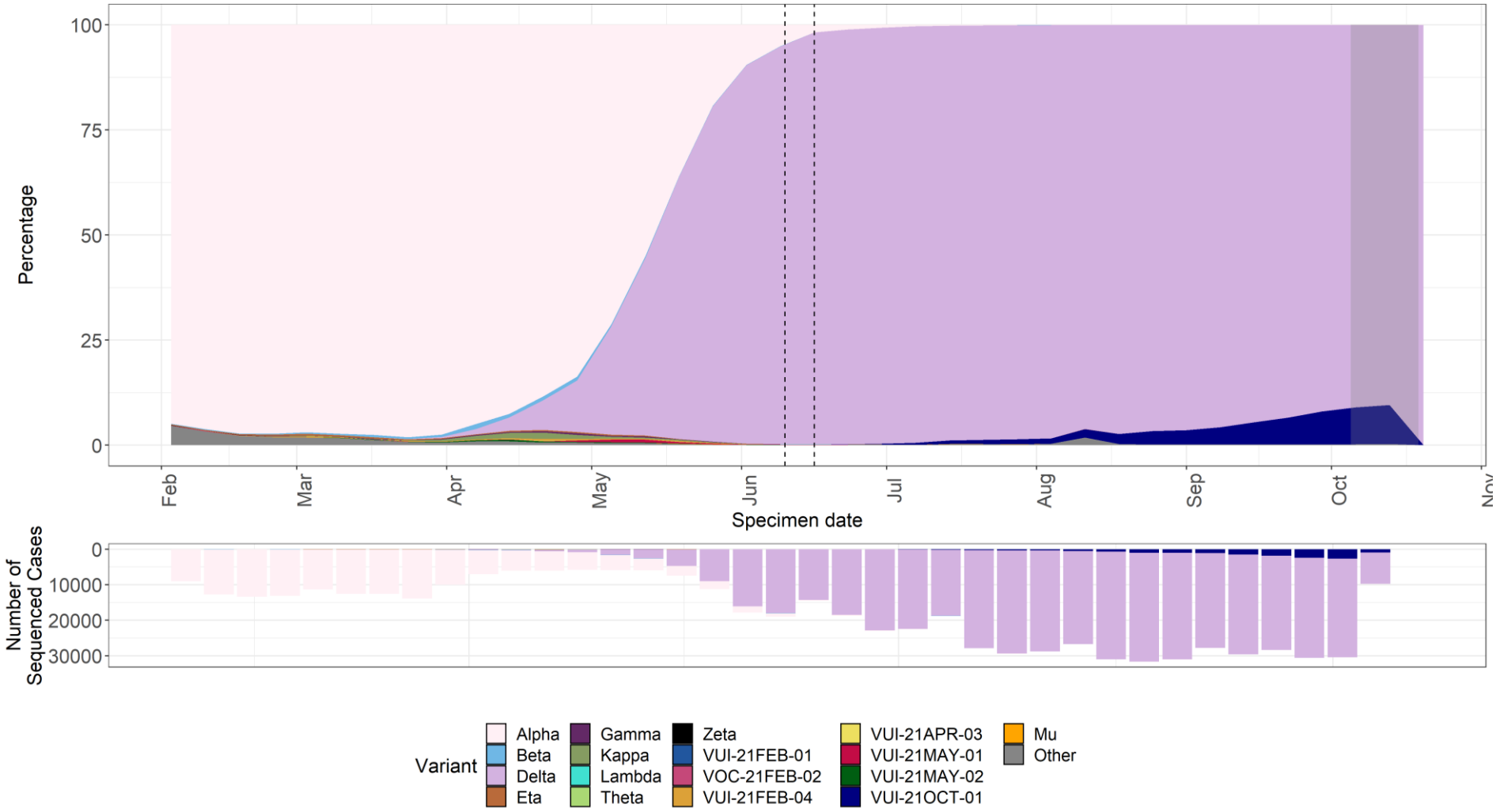


**Figure 5. Variant prevalence plot (all cases in England, genomic surveillance case definitions) by region as of 21 October 2021**

(Find accessible data used in this graph in underlying data.)

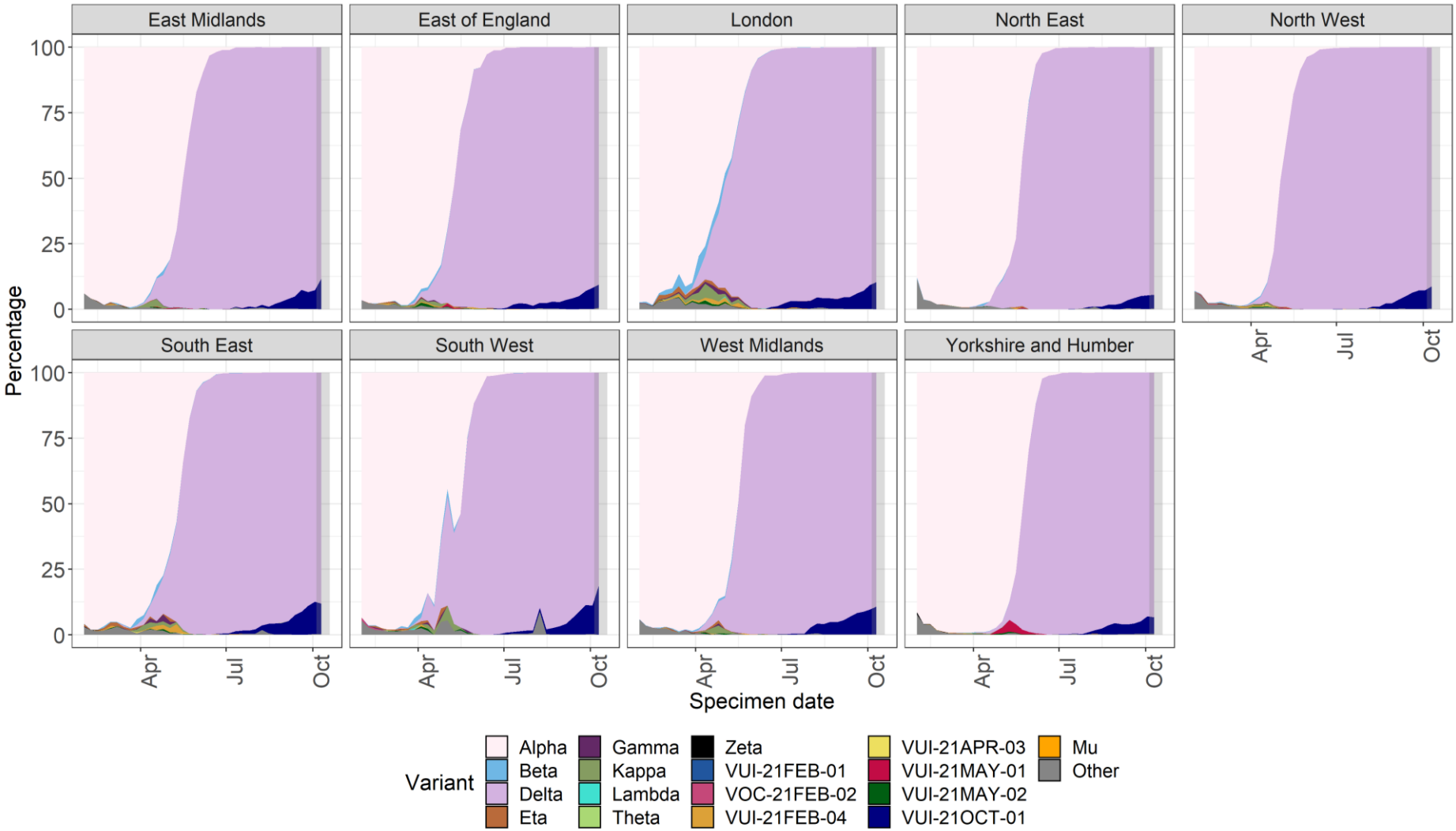
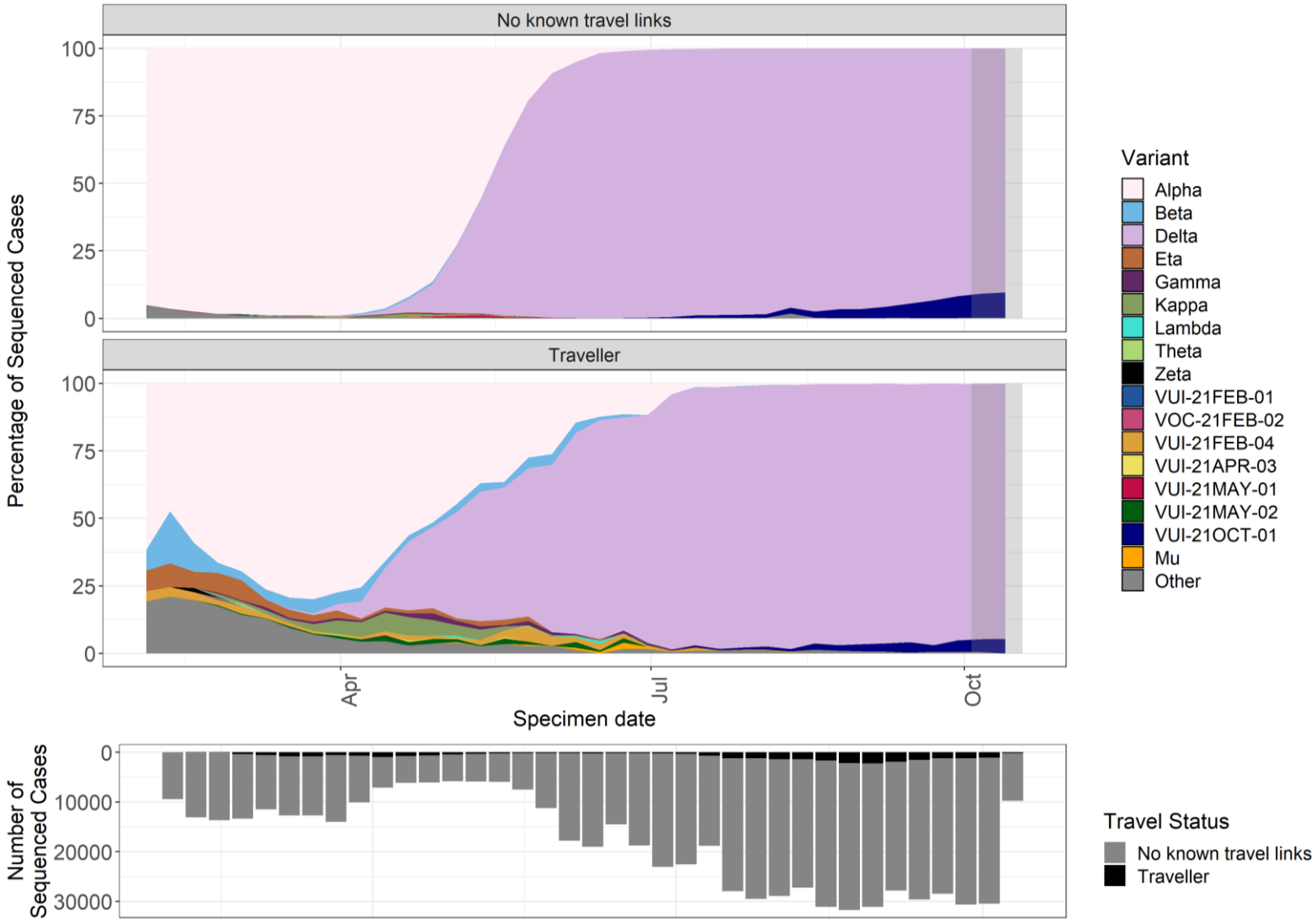
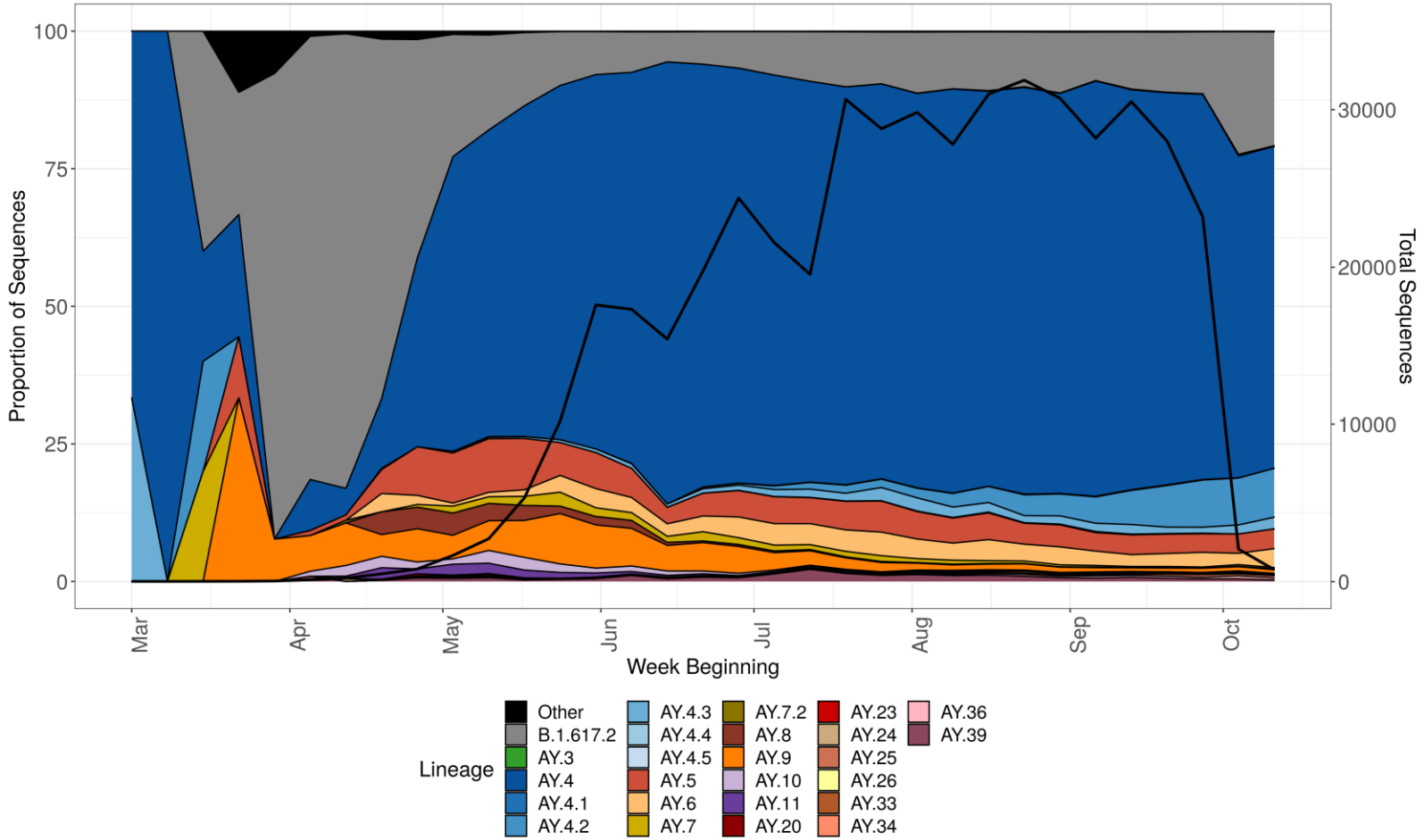


**Figure 6. Variant prevalence plot (all cases in England, genomic surveillance case definitions) by travel status as of 21 October 2021**




Supplementary data is not available for this figure.

**Figure 7. Prevalence of Pangolin lineages within Delta from 1 March 2021 to 20 October 2021 England**
(Find accessible data used in this graph in underlying data.)




The plot excludes 29,532 sequences that were not linked to date information and a further 85 that were not assigned a lineage by Pangolin due to sequence quality. The total number of sequences per week is shown by the black line. Only lineages with more than 100 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”.

**Table 5. Number of confirmed (sequencing) VUI-21OCT-01 cases, by region of residence as of 21 October 2021**

| Region | Confirmed (sequencing) case number | Case Proportion |
|---|---|---|
| East Midlands | 922 | 6.1% |
| East of England | 1,508 | 10.0% |
| London | 2,301 | 15.2% |
| North East | 333 | 2.2% |
| North West | 1,707 | 11.3% |
| South East | 2,973 | 19.7% |
| South West | 1,630 | 10.8% |
| West Midlands | 2,312 | 15.3% |
| Yorkshire and Humber | 1,376 | 9.1% |
| Unknown region | 58 | 0.4% |
| Total | 15,120 | - |

**Figure 8. Cases of VUI-21OCT-01 in England by region as of 21 October 2021**
(Find accessible data used in this graph in underlying data).

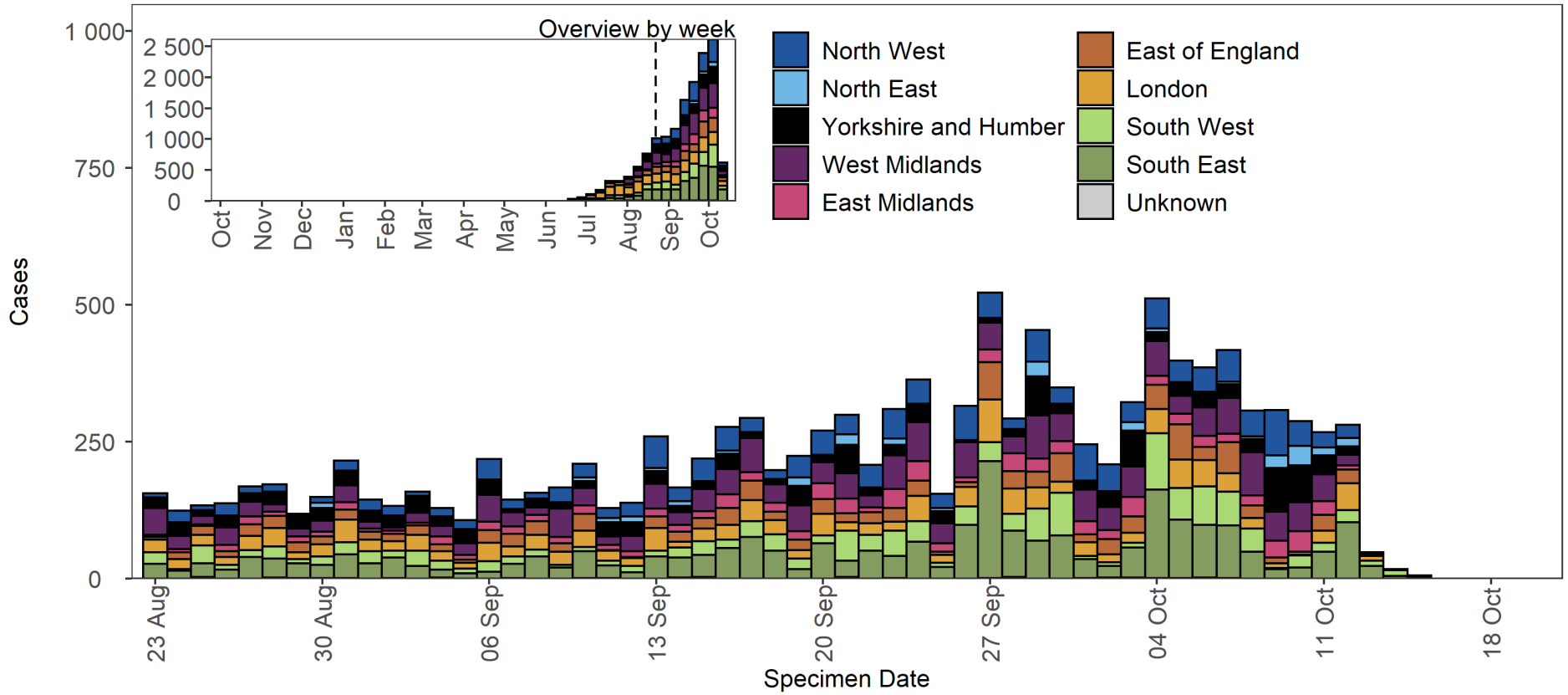
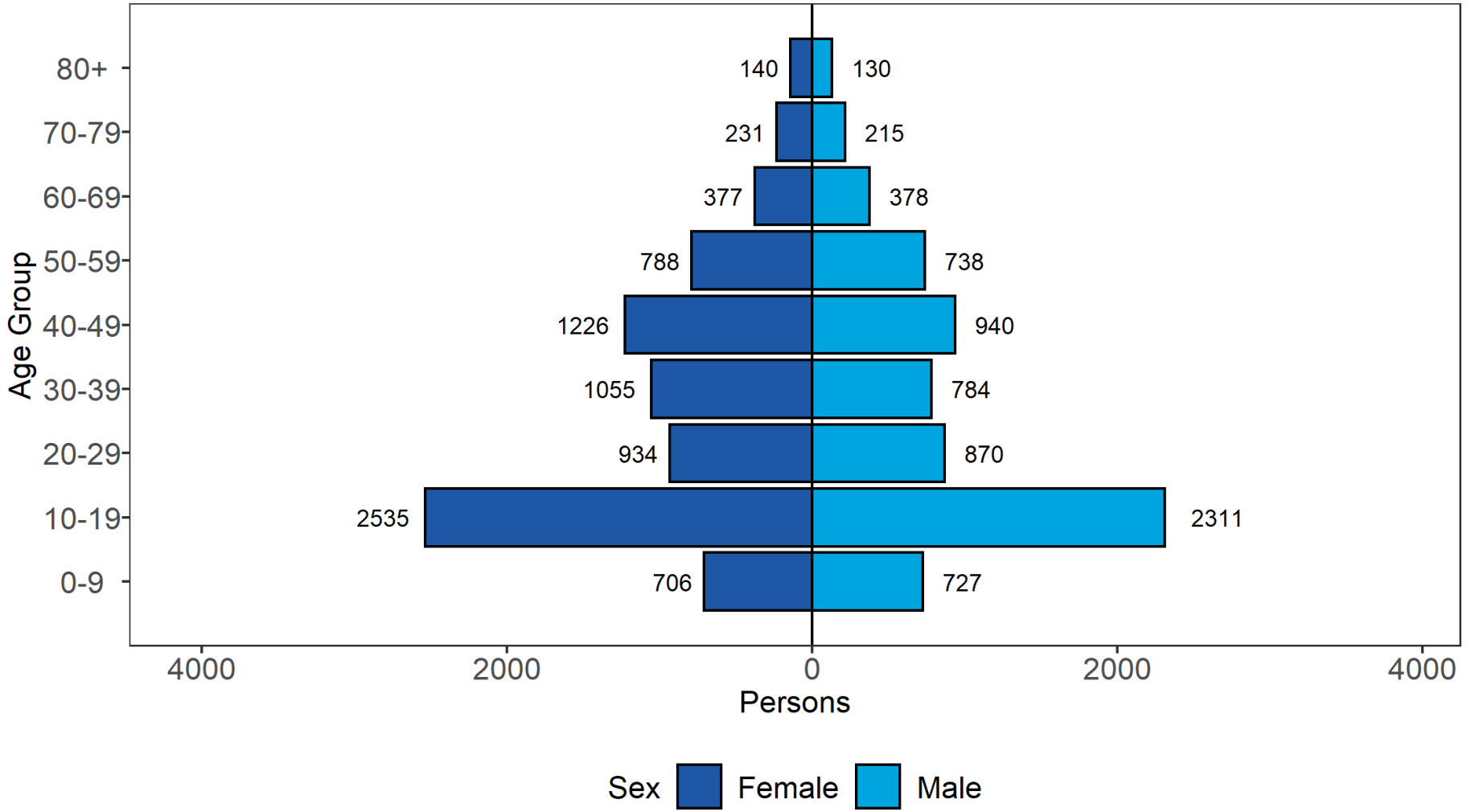


**Figure 9. Age-sex pyramid of confirmed (sequencing) VUI-21OCT-01 cases as of 21 October 2021**
(Find accessible data used in this graph in underlying data)




35 cases excluded where sex or age not reported

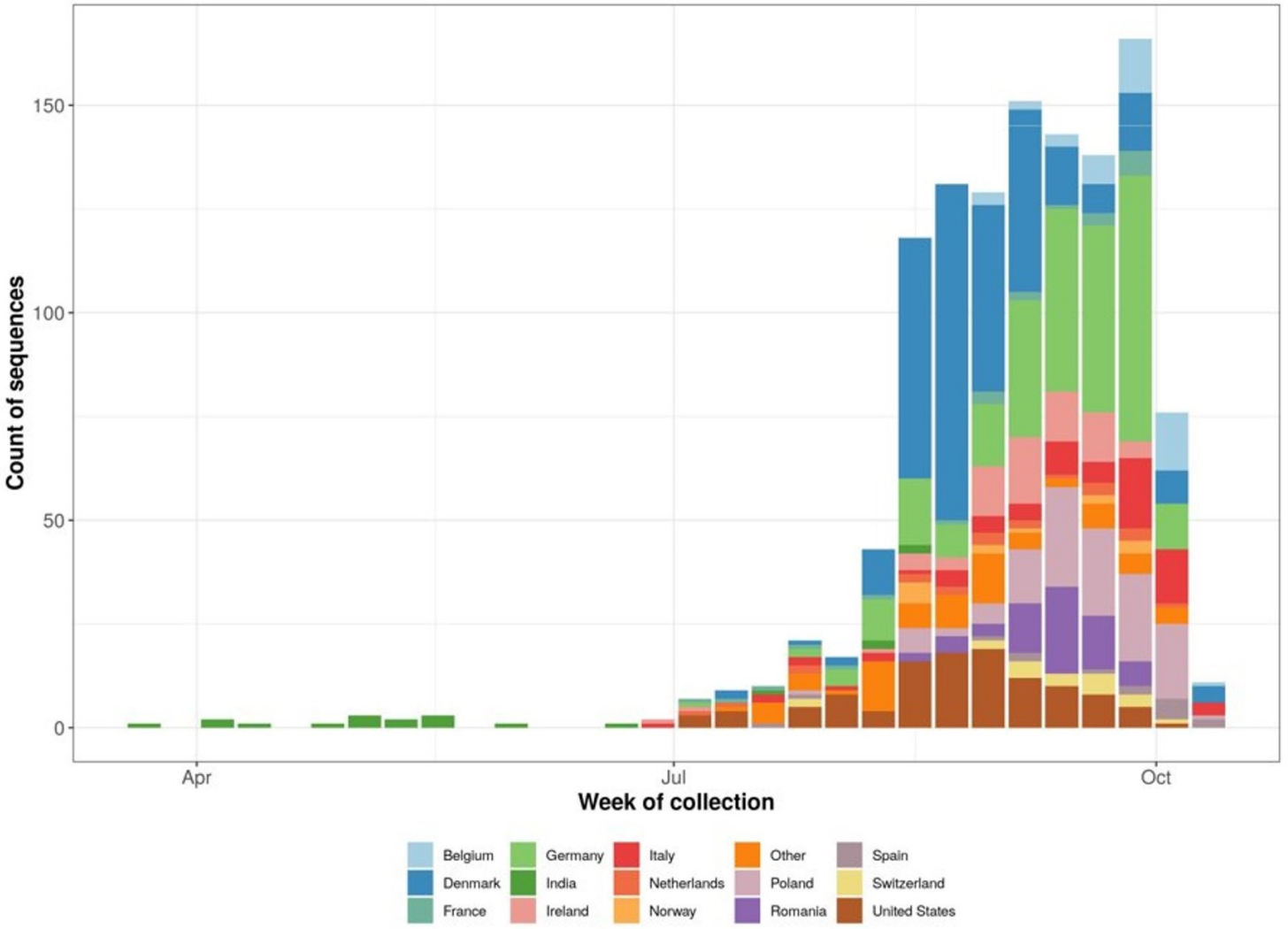
## International epidemiology

As of 20 October 2021, 1,187 sequences on GISAID meet the VUI-21OCT-01 definition from 33 countries (Figure 10). The case definition has not been validated on international data and will be further assessed; results are provisional.

Using the surveillance case definition. sequences are identified from Denmark (291), Germany (253), United States (113), Poland (112), Italy (67), Ireland (66), Romania (61), Belgium (43), France (22), Netherlands (21), India (20), Switzerland (20), Spain (15), Norway (13), Portugal (10), Lithuania (8), Czechia (7), Czechia (7), Malaysia (7), Slovakia (7), Canada (6), Sweden (6), Austria (3), Estonia (2), Finland (2), Greece (2), Iceland (2), Singapore (2), Aruba (1), Australia (1), Bangladesh (1), Bulgaria (1), Japan (1), and Mexico (1).

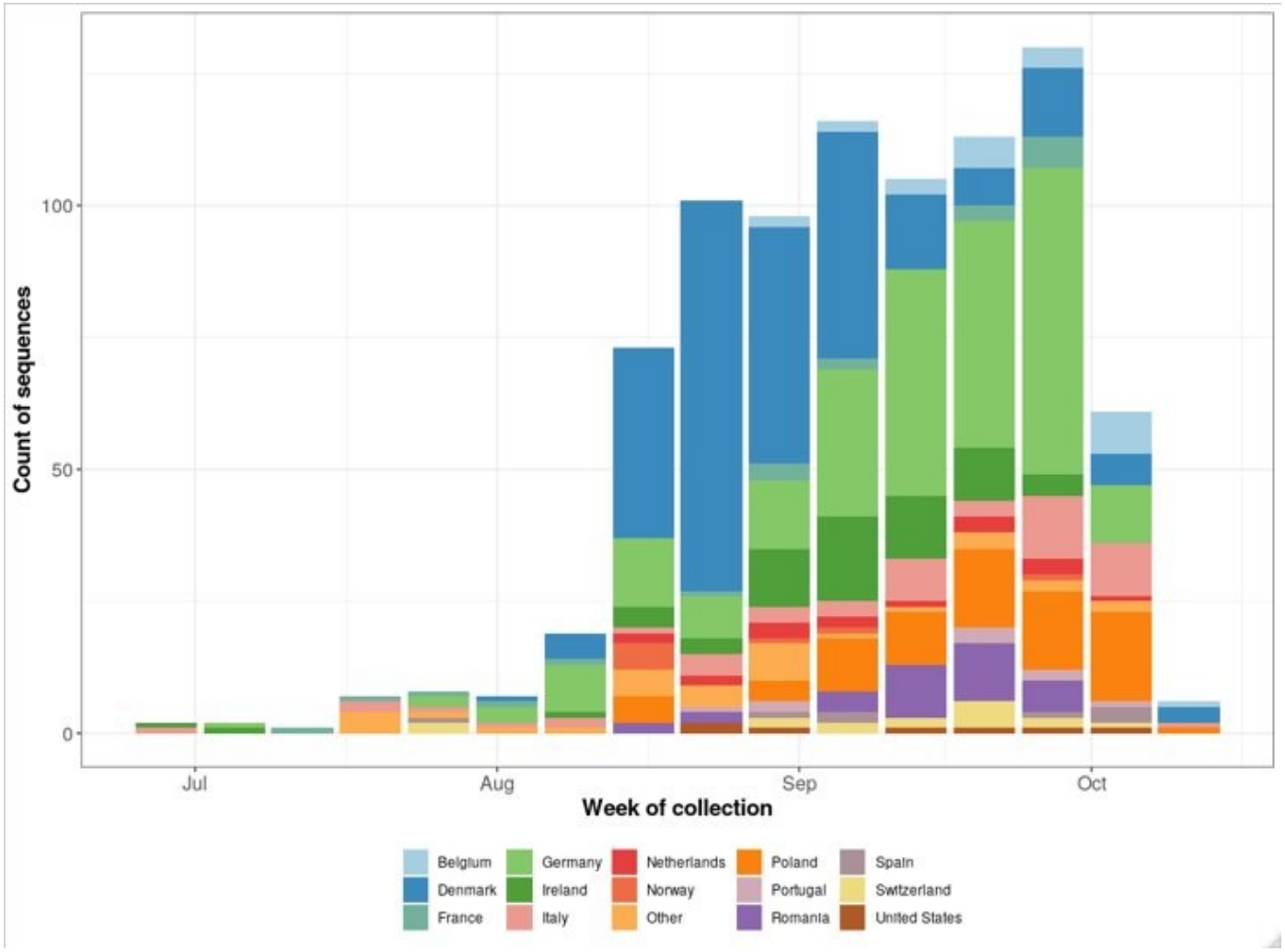
Sequences shown before late June 2021 in Figure 10 meet the VUI-21OCT-01 definition, but do not have an amino acid call at the site 145, and therefore could either be wildtype or mutant. Using a stricter definition requiring all 3 mutations from the VUI-21OCT-01 definition results in 849 sequences present on GISAID as of 20 October 2021, from 27 countries. These data are shown in Figure 11, and a later first week of collection is seen.

**Figure 10. Count of VUI-21OCT-01 classified sequences by week of collection uploaded to GISAID by week as of 20 October 2021** (Find accessible data used in this graph in underlying data)




Countries with 10 or fewer sequences have been grouped together as “Other”.

**Figure 11. Count of VUI-21OCT-01 with all 3 mutations in the definition present, classified sequences by week of collection uploaded to GISAID by week as of 20 October 2021**
(Find accessible data used in this graph in underlying data)

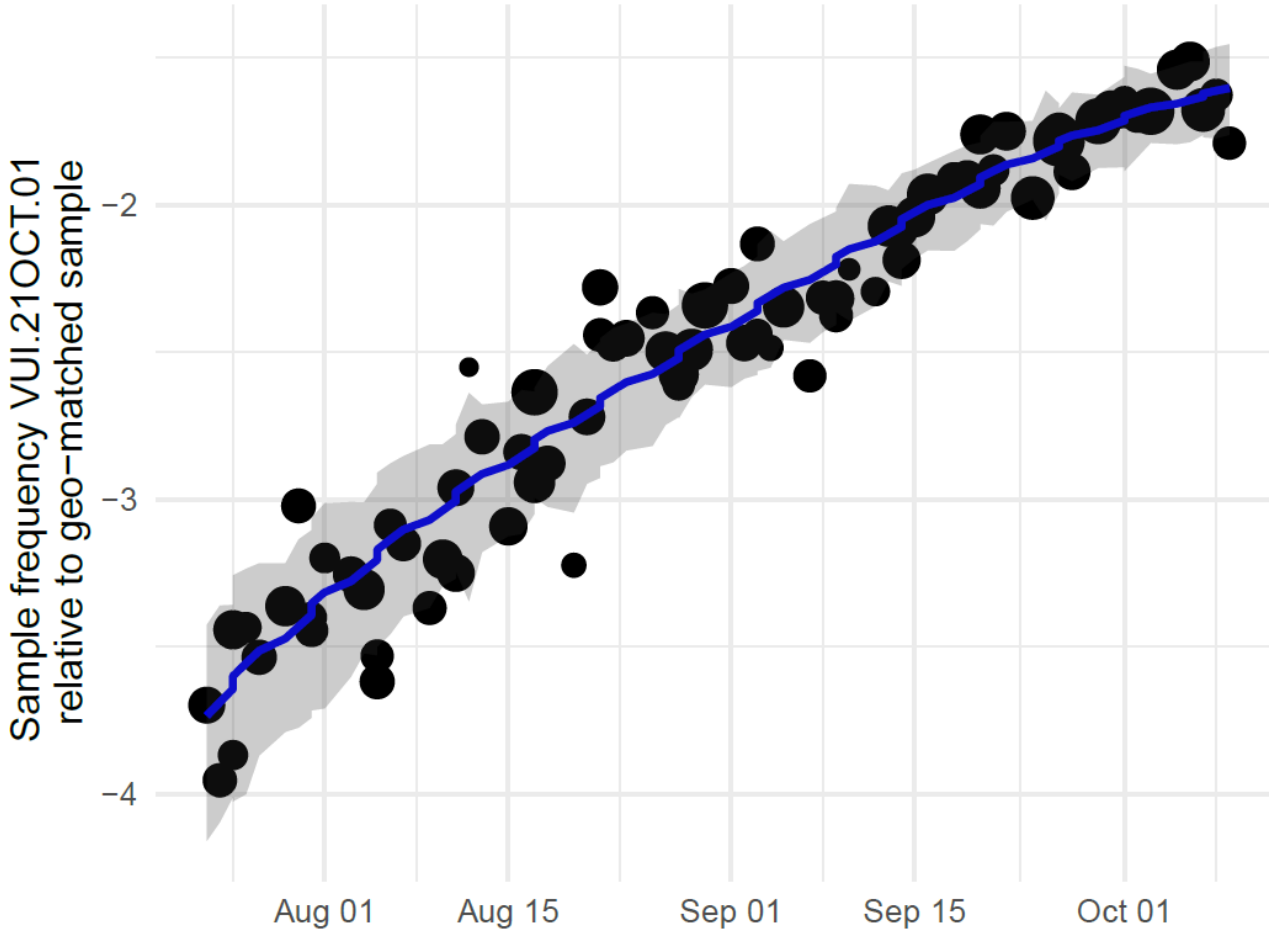



Countries with 5 or fewer sequences have been grouped together as “Other”.

## Growth rate

Logistic growth rates for AY.4.2 for the country as a whole and for each UK region are shown in Figures 12 and 13. Growth rates are computed relative to non-AY.4.2 variants circulating in the same region (geo-matched sample). Sample inclusion criteria are: 1) A non-traveller as determined by matching each case against passenger locator forms and managed quarantine service test codes 2) Collected from Pillar 2 testing. The growth rate is estimated by logistic regression of the variant on time of sample collection. A growth rate of 0 would indicate parity with other circulating variants. Based on a logistic growth model, the country-wide analysis yields a growth rate of 17% for AY.4.2 compared to other circulating variants. Growth rate is context dependent and cannot be interpreted as a change in biological transmissibility.

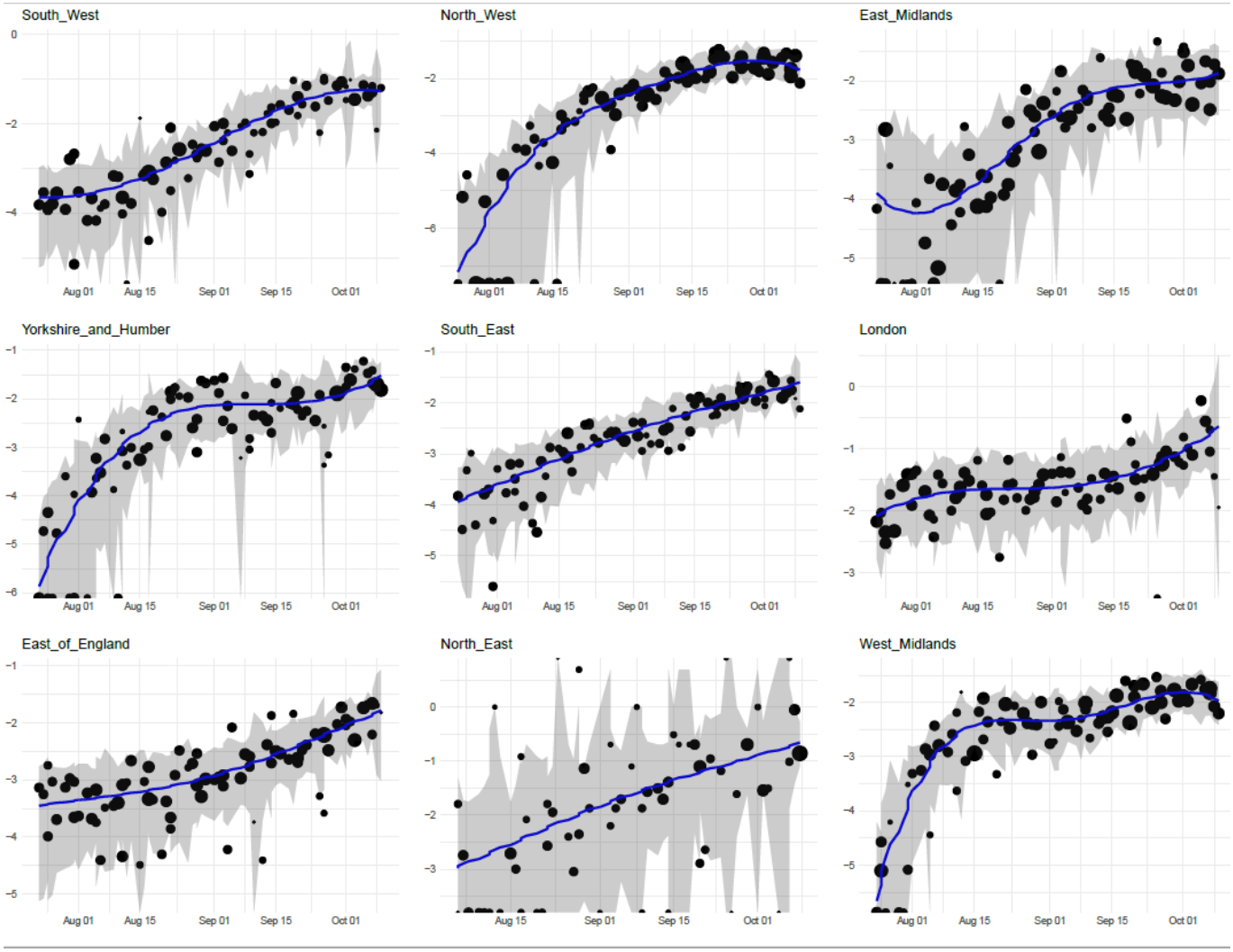
**Figure 12 (single plot) Sample frequency of AY.4.2 as compared to a sample of non-AY.4.2**




Supplementary data is not available for this figure.

The sample frequency of AY.4.2 across the UK has increased since the beginning of August 2021.

**Figure 13 (multiple plots) ) Sample frequency of AY.4.2 as compared to geography-matched sample of non-AY.4.2 for each UK region**




Supplementary data is not available for this figure.

The change in AY.4.2 frequency has not been constant across time or regions.

## Secondary attack rates

Secondary attack rates are based on positive tests amongst contacts named to NHS Test and Trace by an original case identified with a sequenced or genotyped VOC or VUI. This analysis includes secondary attack rates for household and non-household contacts of cases with VUI-21OCT-01 and other Delta cases, from the period 1 August 2021 to 30 September 2021

Delta cases are identified using sequencing results supplemented with genotyping results and exclude low-quality results, VUI-21OCT-01 are identified by sequencing. Secondary attack rates are shown for cases without travel history. Only close contacts named by the original case are included, that is, household members, face-to-face contact, people within one metre of the case for one minute or longer, or people within 2 metres for 15 minutes.

Table 6 shows the secondary attack rates split by type of contact. Secondary attack rate for household contacts of cases with VUI-21OCT-01 was 12.4% (95% CI: 11.9% to 13.0%), higher than that observed for other Delta cases where it was 11.1% (95% CI: 11.0% to 11.2%). In non-household settings, the secondary attack rate was higher for VUI-21OCT-01 than other Delta cases, but this difference was not significant. No significant variation between regions was observed.

**Table 6. Secondary attack rates for contacts of non-travel cases with VUI-21OCT-01 and other Delta**
(1 August 2021 to 30 September 2021, Delta data as of 18 October 2021, VUI-21OCT-01 data as of 15 October 2021 and contact tracing data as of 21 October 2021)

| Variant | Non-travel cases (with contacts) | Secondary attack rate in household contacts of non-travel or unknown cases (95% CI) [secondary cases/contacts] | Secondary attack rate in non-household contacts of non-travel or unknown cases (95% CI) [secondary cases/contacts] |
|---|---|---|---|
| VUI-21OCT-01 | 7,492 (73.7% with contacts) | 12.4% (11.9% - 13.0%) [1,653/13,326] | 4.4% (3.8% - 5.1%) [167/3,781] |
| Delta excluding VUI-21OCT-01 | 377,708 (71.6% with contacts) | 11.1% (11.0% - 11.2%) [69,811/628,453] | 4.0% (4.0% - 4.1%) [7,457/184,419] |

# Sources and acknowledgments

## Data sources

Data used in this investigation is derived from the COG-UK and UKHSA genomic programme dataset, the UKHSA Second Generation Surveillance System (SGSS), the Secondary Uses Service (SUS) dataset, Emergency Care Data Set (ECDS), and the UKHSA Case and Incident Management System (CIMS). Data on international cases are derived from reports in GISAID, the media and information received via the International Health Regulations National Focal Point (IHRNFP) and Early Warning and Response System (EWRS).

## Repository of human and machine-readable genomic case definitions

Genomic definitions for all VOC and VUI are provided in order to facilitate standardised VOC and VUI calling across sequencing sites and bioinformatics pipelines and are the same definitions used internally at UKHSA. Definition files are provided in YAML format so are compatible with a range of computational platforms. The repository will be regularly updated. The genomic and biological profiles of VOC and VUI are also detailed on first description in prior technical briefings.

## Variant Technical Group

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UKHSA Outbreak Surveillance Team
UKHSA Epidemiology Cell
UKHSA Contact Tracing Data Team
UKHSA International Cell
Contributions from the Variant Technical Group Members including the Genotype to Phenotype Consortium

### Variant Technical Group members and contributors

The UK Health Security Agency Variant Technical Group includes members and contributors from the following organisations: UKHSA, Public Health Wales, Public Health Scotland, Public Health Agency Northern Ireland, the Department of Health and Social Care, Imperial College London, London School of Hygiene and Tropical Medicine, University of Birmingham, University of Cambridge (including the MRC Biostatistics Unit), University of Edinburgh, University of Liverpool, the Wellcome Sanger Institute, Genotype to Phenotype Consortium, SPI-M.

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