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Briefing note: Potential community transmission of B.1.617.2 inferred by S-gene positivity.

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Preliminary analysis. Draft for discussion. Not peer reviewed.

Background

- S-gene positive cases (S+) have been exponentially increasing since the end of March, compared to decreases in S-gene negatives (S-), despite the overall number of cases declining.
- Sequencing results are coming for the majority of Pillar 2 tests but with significant delay.

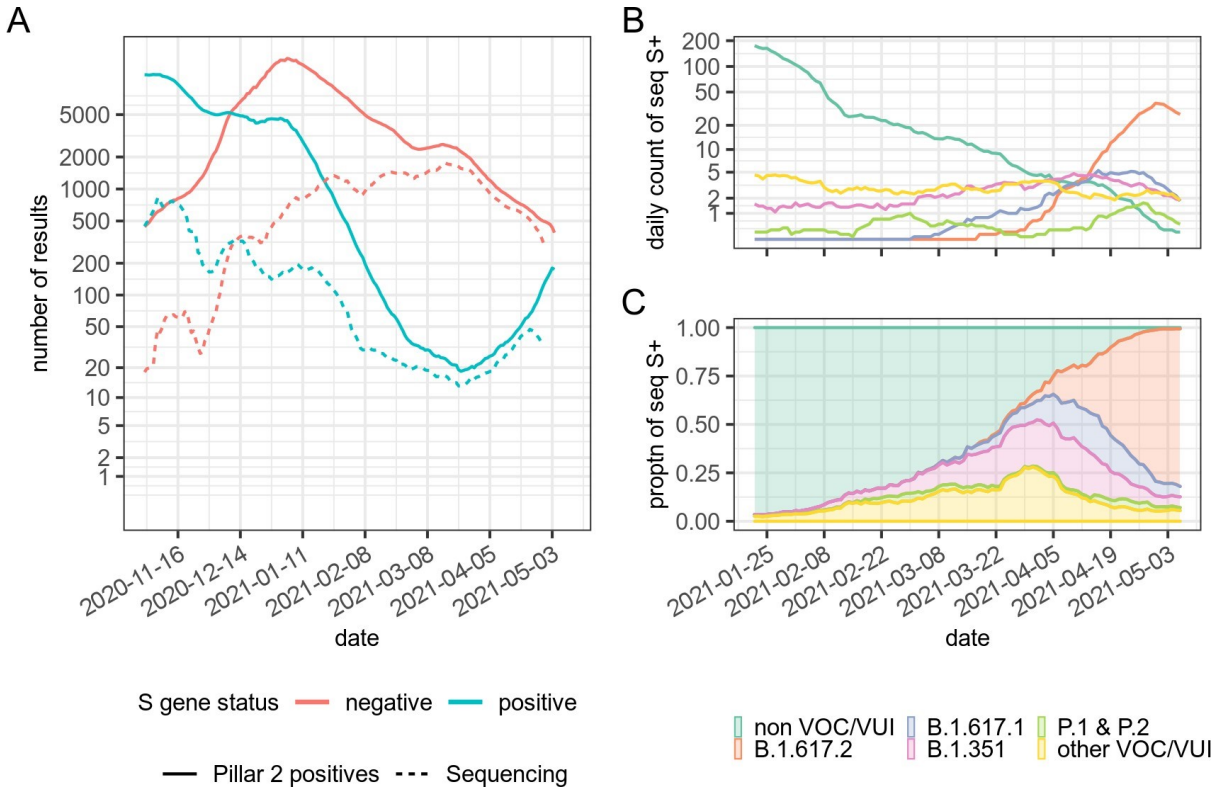


Figure 1: Timeline of cases, broken down by S-gene status (panel A), sequencing (panel B), and proportion of S-gene positive cases identified as a VUI/VOC (panel C).

- Recent sequencing results of S-gene positive cases has been dominated by B.1.617.2.
- Given the number of S+ cases that have yet to be sequenced and are in the pipeline, the current data understates the size of the B.1.617.2 outbreak.

- S-gene positive cases are an evolving mixture of different strains but since late March have been more likely than not to be a VOC or VUI when later sequenced.
- Since May all S+ cases have been a VOC or VUI when sequenced

Geographic distribution of cases

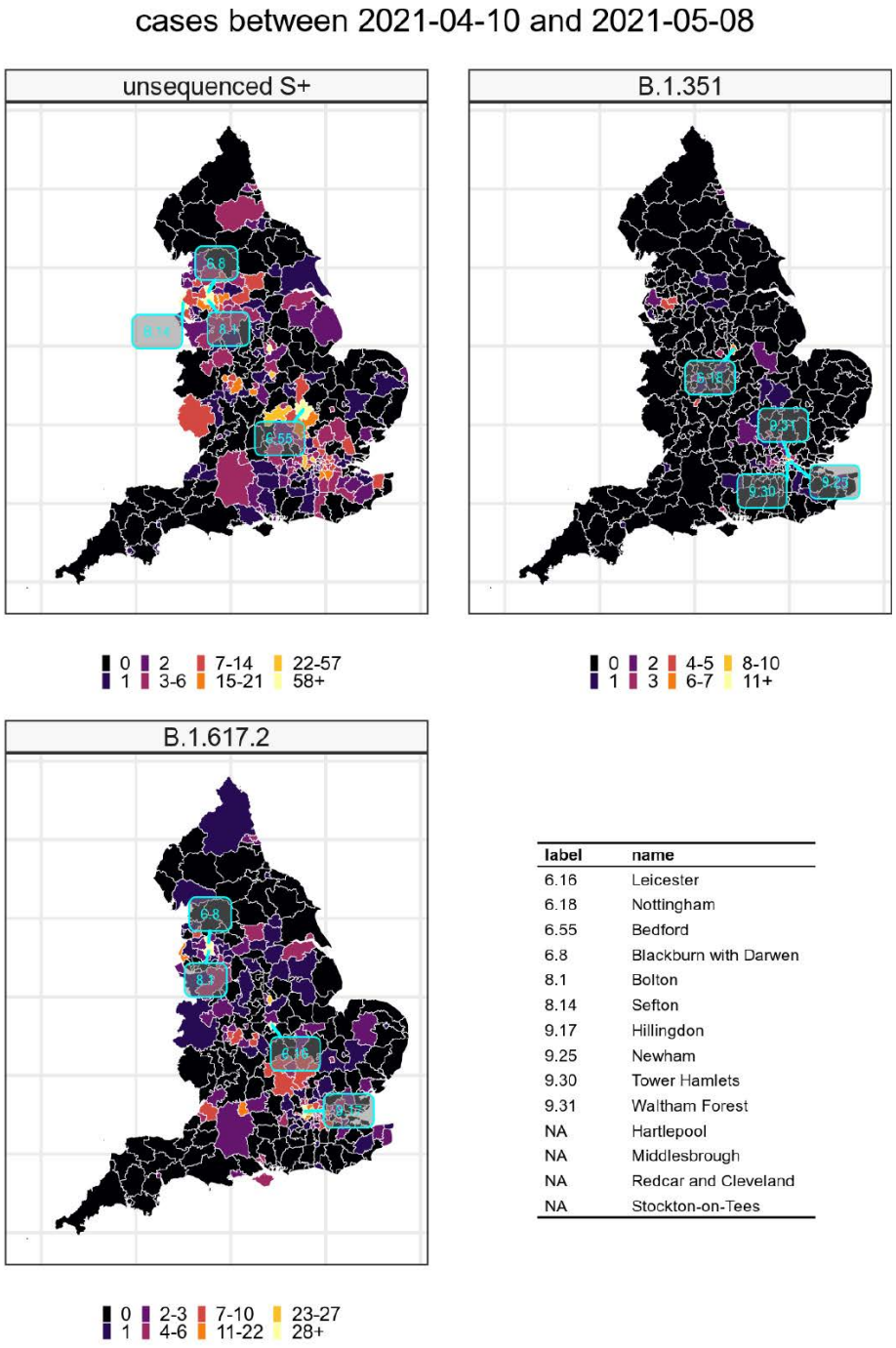


Figure 2: Maps of cases between 10 April and 8 May 2021: (top left) unsequenced S-gene positive cases, (top right) sequenced B.1.351 (bottom left) sequenced B.1.617.2

name	unsequenced S+	B.1.617.1	B.1.617.2	B.1.351	other
Bolton	336	-	110	5	1
Blackburn with Darwen	98	-	40	-	3
Sefton	110	1	16	-	-
Leicester	56	17	42	1	1
Nottingham	58	-	25	6	2
Bedford	77	-	10	-	-
Hillingdon	30	2	29	2	5
Brent	26	4	24	2	5
Newham	11	3	22	10	11
Hounslow	19	11	18	2	6
Tower Hamlets	8	2	9	28	8
Ealing	5	3	26	3	4
South Northamptonshire	27	-	7	-	-
Birmingham	17	3	7	1	3
Croydon	20	-	6	-	5
Coventry	15	3	10	2	2
Harrow	3	4	21	-	3
Redbridge	12	3	4	3	6
Wigan	21	-	3	4	-
Bromley	16	2	6	-	2

Table 1: list of areas where S+ cases have been observed, and corresponding numbers of sequenced VOC/VUIs. (N.b. Some small number entries below 10 have been removed to preserve anonymity.)

- Areas with the highest burden of S+ are co-located with high incidence of B.1.617.2
- 2 concerning areas around NW of Manchester have been observed (Bolton & Blackburn, and Sefton & Liverpool), and a new rapidly growing cluster in areas surrounding Bedford.
- Also Leicester, Nottingham, and West London of concern
- Outbreaks of B.1.351 in East London have also been observed but not growing.
- S-gene status available quicker than sequencing, so provides a leading signal.
- Areas where S+ status is not available do not appear in these lists (see appendix). They could have substantial B.1.617.2 burden which we are not detecting.

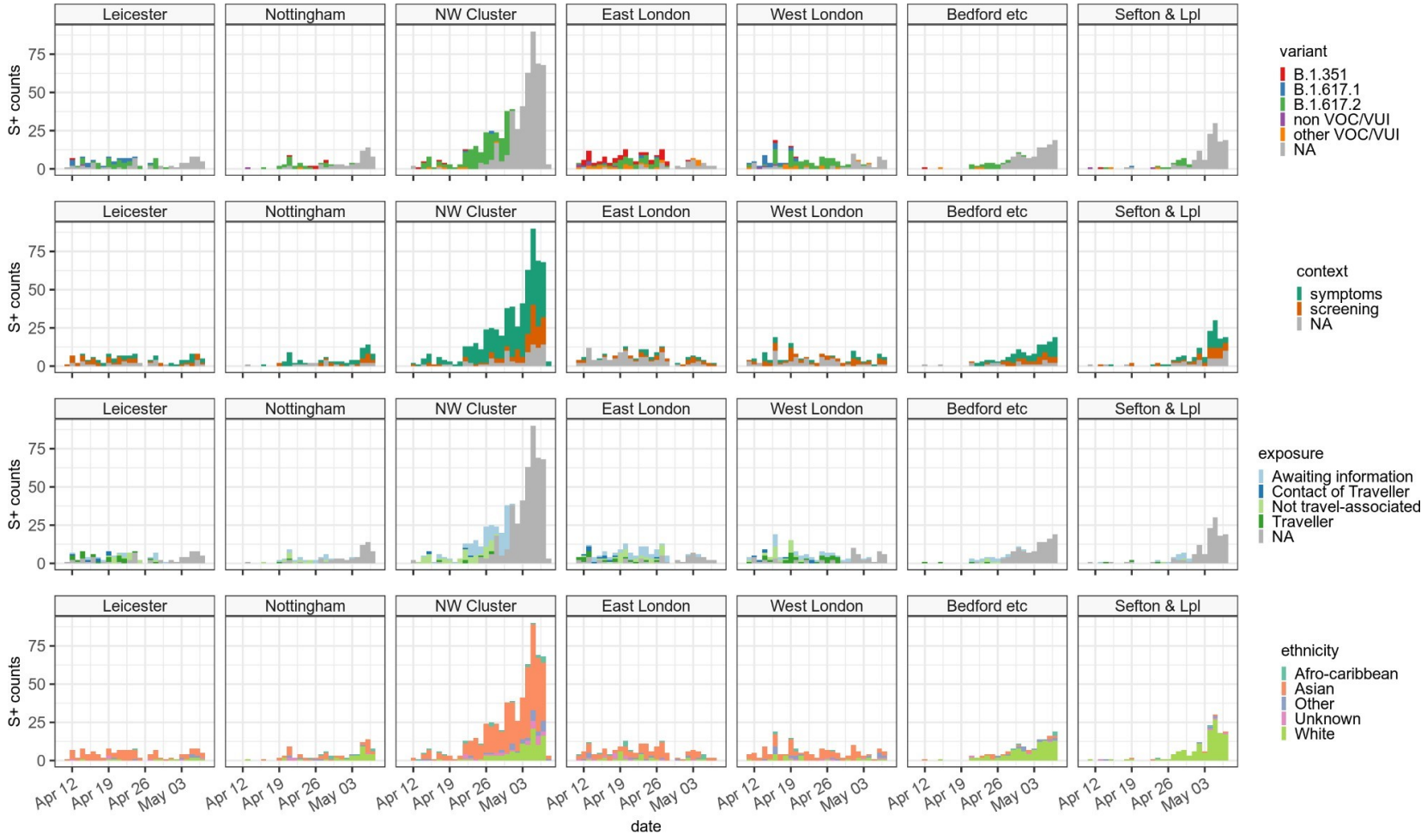


Figure 3: Case counts in sequenced data broken down by sequenced variant status (top panel), context of test (second panel), exposure (third row) and ethnicity (final row) Data includes figures up to the 8th May 2021 based on S-gene data supplied on 10th May 2021

- In figure 3 by combining S-gene positive and sequence proven S+ VOC cases we see cases in the NW Cluster, Bedford and Sefton are increasing apparently exponentially.
- Cases in the NW Cluster, Bedford and Sefton regions are largely B.1.617.2 on sequencing. They are typically detected as a result of symptomatic disease. Exposure information is not suggestive of importation. Although Bolton was initially dominated by cases in the Asian population, there is now a heterogeneous mix of cases, suggesting community spread.
- In other areas picture is more mixed. This is confused by the fact that S-gene TaqPath testing is not done at high rates in these regions.

Growth rate estimation

- We estimate growth rates of observed symptomatic S+ or S- cases by fitting a poisson model to a sliding window of 8 weeks data. Estimates are unstable with smaller windows as the cases reach very small numbers before the recent increases. 8-week growth rates will underestimate recent changes. Note that between early March and early April most S+ cases are not VoC/VuI. After early April the proportion of S-gene positive cases that are due to variant of concern increases (see the first figure in this document).
- We have three areas that we think are principally community transmission of B.1.617.2 - NW cluster (Bolton), Sefton & Lpl, Bedford etc. Growth rate estimates for these regions are shown in Figure 4.

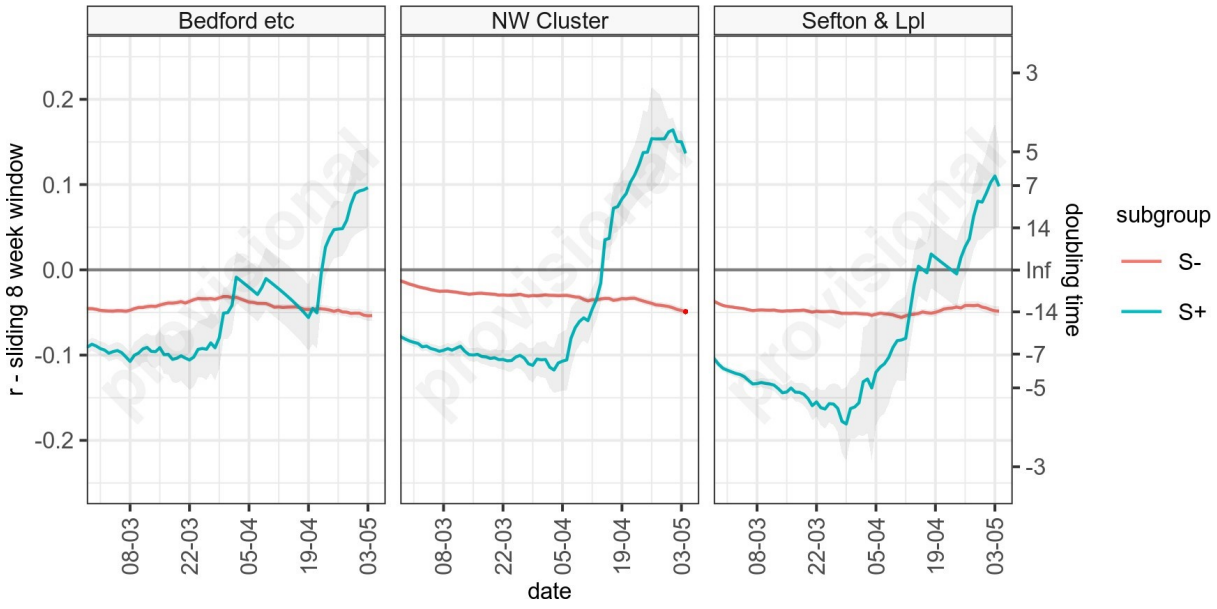


Figure 4: Growth rate estimates broken down by S-gene status in 3 locations which seem likely to be community transmission of principally B.1.617.2.

- We have another three areas where the picture is mixed, and some evidence of import, and probably some local transmissions, but which are dominated by B.1.617.2. These are Leicester, Nottingham, and West London, and shown in Figure 5

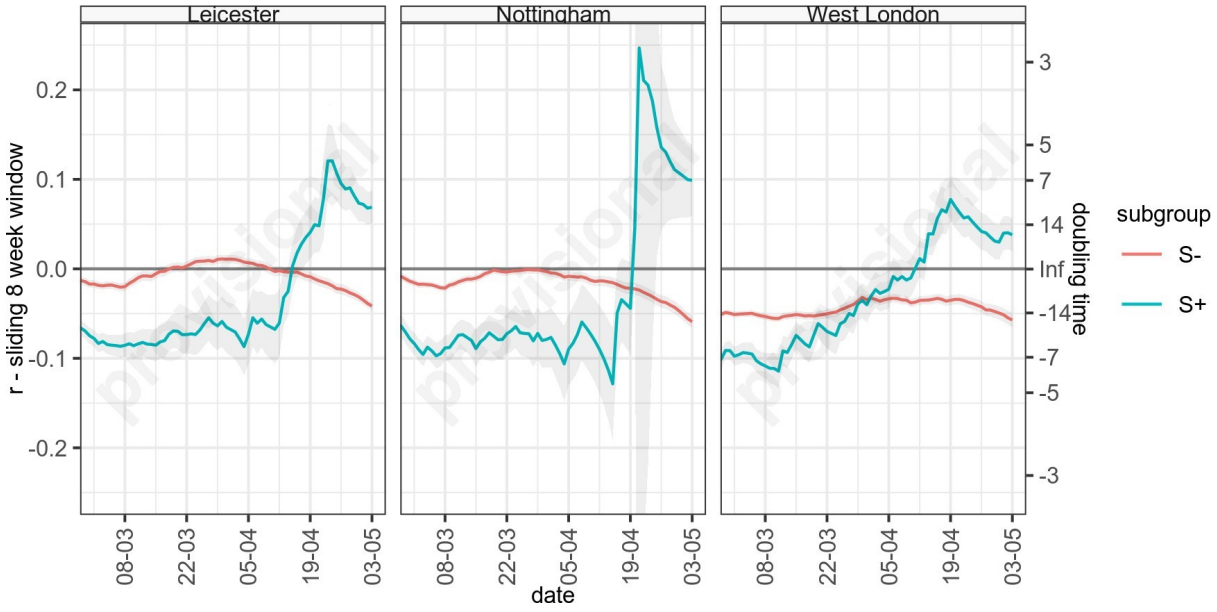


Figure 5: Growth rate estimates broken down by S-gene status in 3 locations which are more mixed in terms of variants detected and exposure risks.

- We have one area where the majority of variant cases are B.1.351 in East London, and the cases will be mixed importation and community transmission.
- Although growth seems less significant here this may be biased by the fact that S-gene status is not uniformly performed across the country, and coverage rates are lower in London compared to the regions considered above.

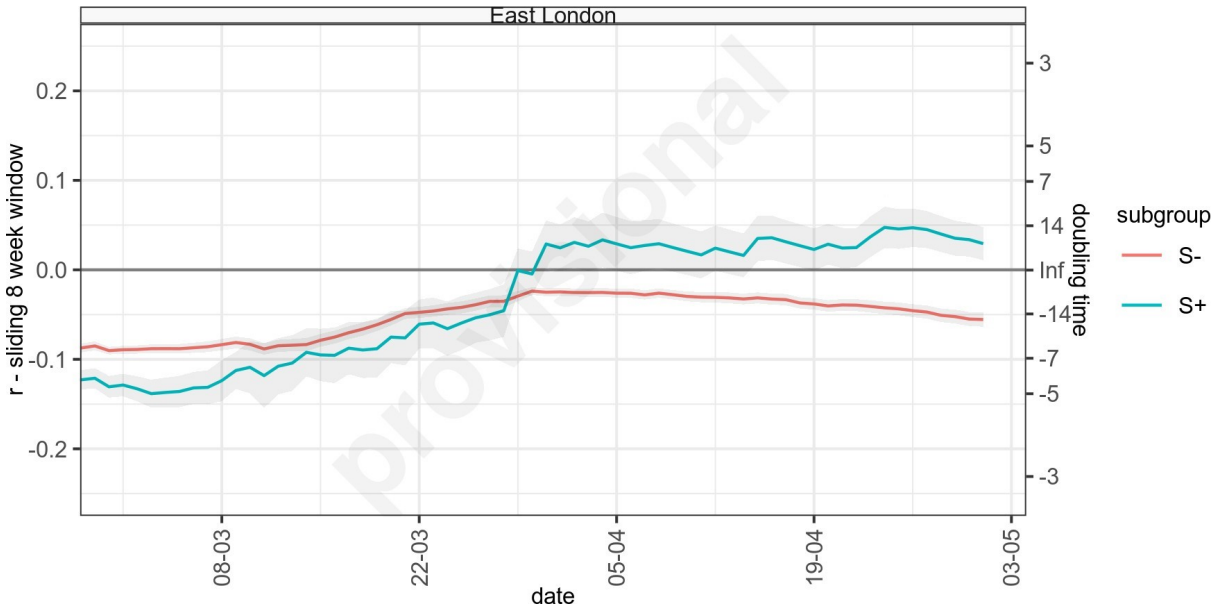


Figure 6: Growth rate estimates broken down by S-gene status in the location which has the most B.1.351.

- For comparison we calculate growth rate for S+ cases across all of England, which will be a mix of all different variants, importations and community cases.

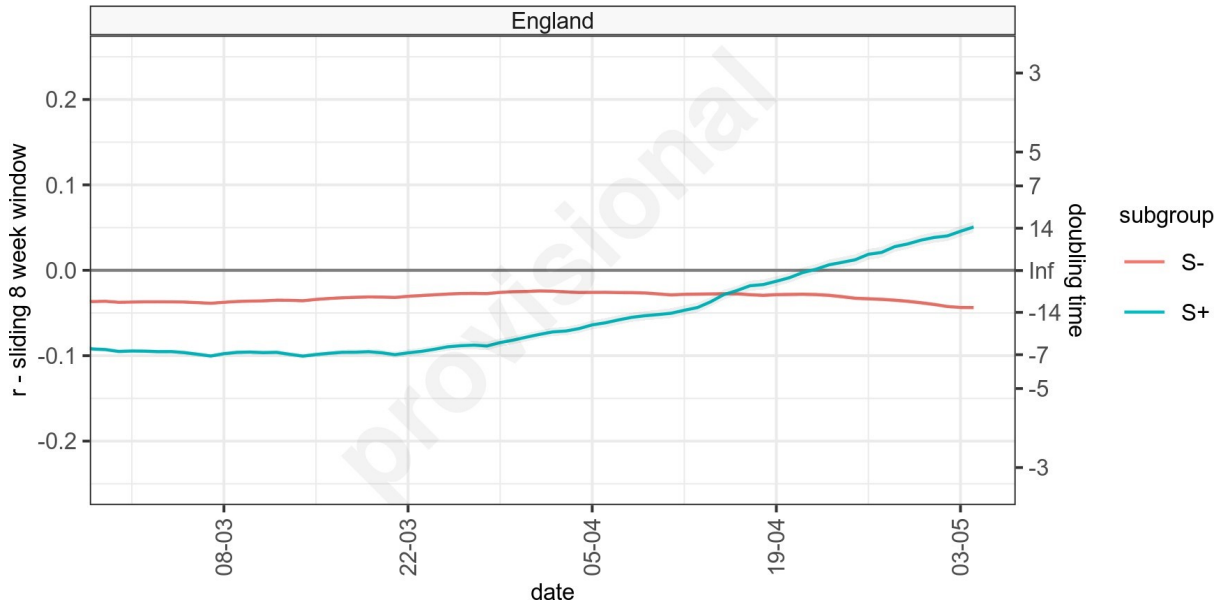


Figure 7: Overall growth rate for England.

- Both symptomatic or all S+ cases produce qualitatively similar results (N.B. symptomatic cases shown for all areas).
- In NW Cluster, Sefton and Bedford, where community transmission is expected, S+ cases are doubling every approx 7 days.
- In Leicester, Nottingham, West London, where the pattern is more mixed, doubling of case numbers is shortened but not to the same extent.
- Alternative methods for estimating the growth rate (see Appendix) show broadly similar patterns.

Limitations

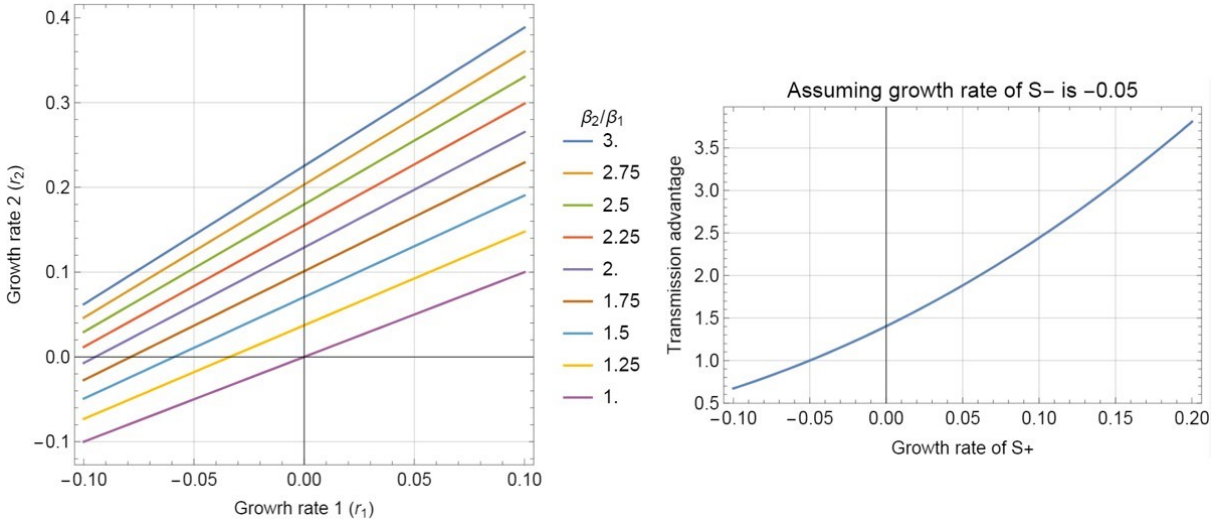
- We cannot conclude with certainty this represents increased transmissibility of B.1.617.2 as other circulating VOCs or wild-type are also included in the S+ signal, as are occasional B.1.1.7.
- We do not know if the increase in transmissibility is the result of specific mixing patterns, or super-spreading events.
- S-gene positive and S-gene negative cases are potentially in very different populations, with different mixing habits.
- We don't have traveller status data linked, unless the case has been sequenced, so there is potentially a large bias from imported cases in the S+ data.
- TaqPath testing coverage is not uniform - the proportion of Pillar 2 cases that have a S-gene result is much higher in the North West and Midlands. S-gene status is unknown for cases in the SW and SE. There may be higher rates of VOCs in London than suggested by the S-gene data.
- We don't know if there was intensive PHE case finding activity in areas which would have biased case acquisition.
- There is uncertainty at the end of the growth rate time series, but also potential reporting delays, in the input data, which we have not corrected for. Some growth rate models suggest some levelling off is possible, but more data is required.

Further directions:

- Analysis of the vaccination status and previous infection status of new S-gene positive and newly sequenced B.1.617.2 cases is needed.
- We are developing spatiotemporal models to identify areas where we expect to see high cases of specific variants, or where specific S-gene positive cases are at high risk of being a specific variant, to assist targeting interventions

Discussion:

- SPI-M Roadmap modelling suggests new variants with increased transmissibility are capable of generating a wave of infections bigger than previous waves.
- Incontrovertible evidence that B.1.617.2 is more transmissible may come too late.
- It is possible the outbreak in India is partly the result of higher transmission of B.1.617.2.
- In the face of uncertain evidence the risk of over-reacting seems small compared to the potential benefit of delaying a third wave until more people are vaccinated.
- Rapid containment in Bolton and Blackburn, Sefton, Liverpool, and the area around Bedford is warranted. Surge testing for B.1.617.2 in these areas is needed.
- Active surveillance for further outbreaks using S-gene positive tests results is valuable, and should be extended to any areas that are not currently being tested with the TaqPath assay.
- Aggressive use of asymptomatic testing, contact tracing and isolation of S-gene positive cases in targeted areas in the rest of the country may be needed to contain or delay outbreaks.
- Surge vaccination is worth considering, however protection will take time to develop, so may not be enough on its own. Surge vaccination will redistribute vaccines, and require increased local resources, may not be achievable if growth continues.
- We can translate a difference in growth rates, using the following quick conversions. This assumes the same generation times for S-gene positives and negatives. If the S-gene positives have a growth rate of -0.05, then we see that positive growth of S-gene positives implies a transmission advantage of more than 1.4 times the S-gene negatives.



Appendix

Definition of areas under analysis:

area	code	name
Leicester	E06000016	Leicester
	E07000135	Oadby and Wigston
	E07000131	Harborough
Nottingham	E06000018	Nottingham
NW Cluster	E08000001	Bolton
	E06000008	Blackburn with Darwen
	E07000123	Preston
East London	E09000025	Newham
	E09000002	Barking and Dagenham
	E09000031	Waltham Forest
	E09000030	Tower Hamlets
	E09000012	Hackney
West London	E09000018	Hounslow
	E09000015	Harrow
	E09000005	Brent
	E09000013	Hammersmith and Fulham
Bedford etc	E06000055	Bedford
	E07000155	South Northamptonshire
	E06000042	Milton Keynes
Sefton & Lpl	E08000014	Sefton
	E08000012	Liverpool
	E08000011	Knowsley

Growth rate estimation - alternate method 1: As an alternative approach, we estimate growth rates of observed symptomatic S+ or S- cases by fitting a Gaussian process and a weekday random effect into a negative binomial model. The growth rate is estimated for the following areas: Bedford, NW Cluster, Sefton & Lpl, Leicester, Nottingham, West London, East London, England, and an aggregate of the areas not included.

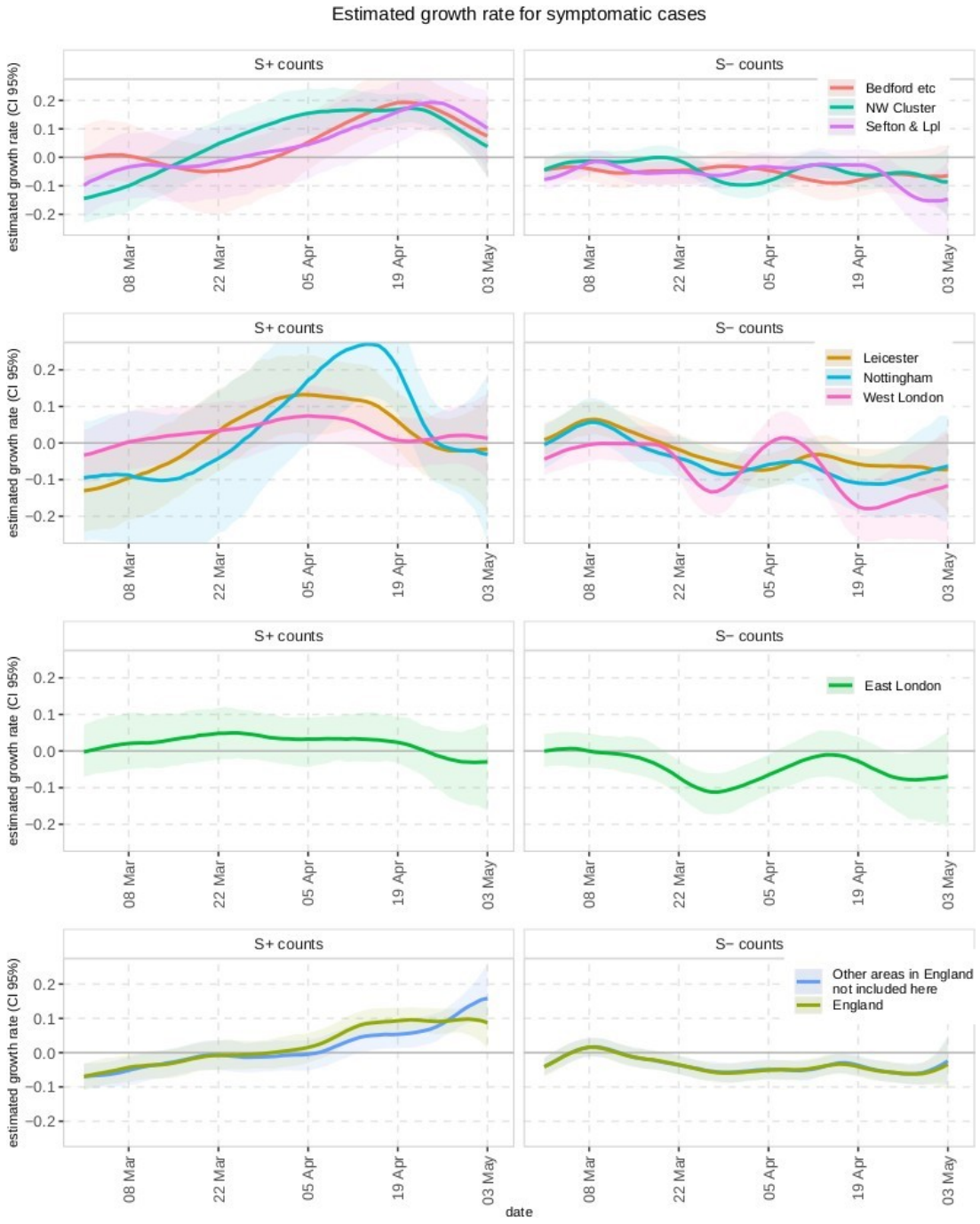


Figure A1: Estimated growth rates limited to symptomatic cases. Left column shows S-gene positive growth rates, left column shows S-gene negative cases. Rows denote different regions, with England on the bottom row.

- The same estimation method was applied to the observed S+ and S- including symptomatic and asymptomatic cases.

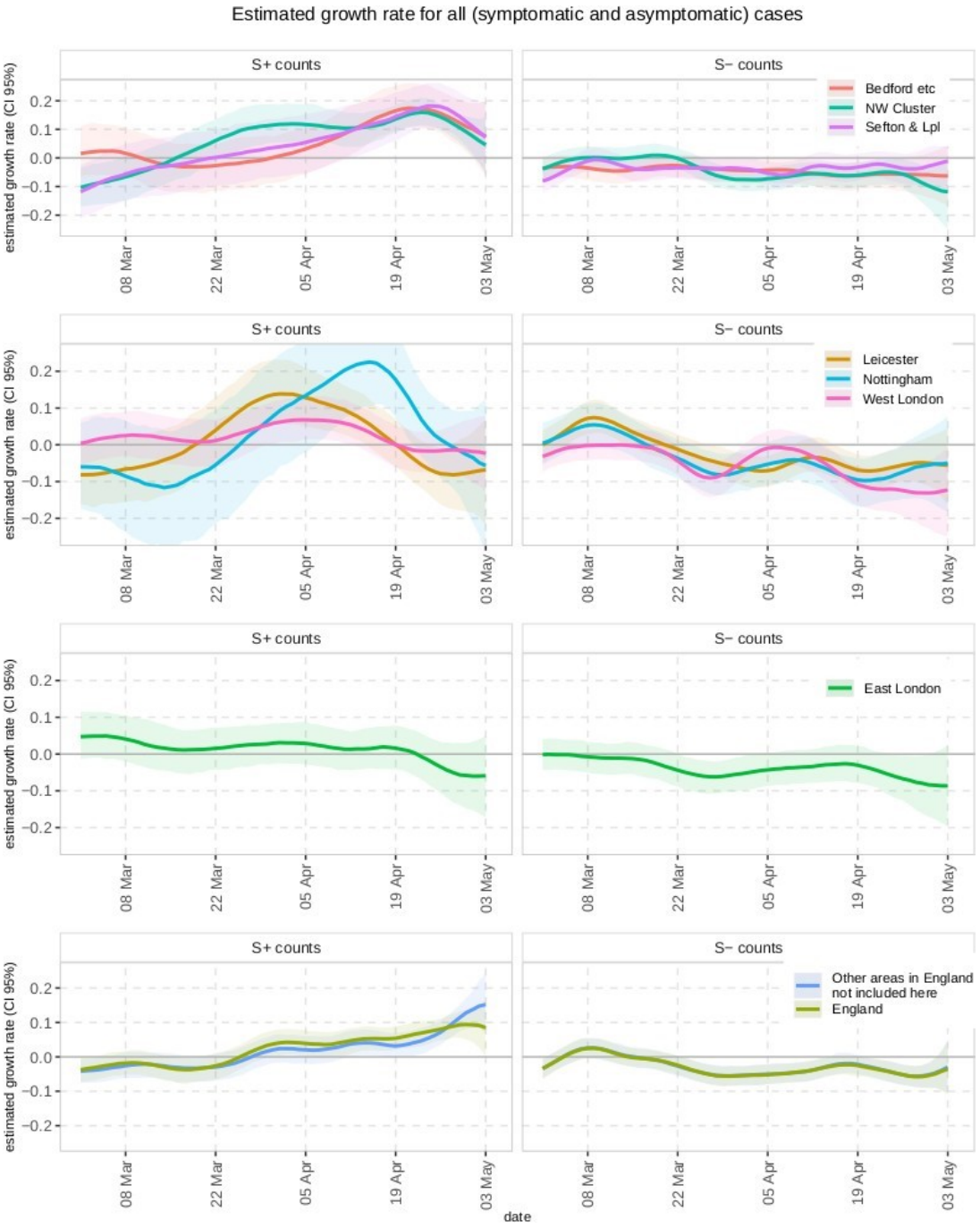


Figure A2: Estimated growth rates from all cases. Left column shows S-gene positive growth rates, left column shows S-gene negative cases. Rows denote different regions, with England on the bottom row.

- We find the same general pattern of increased growth in S positive cases in areas that we are concerned about community transmission, in particular Bedford, the NW cluster including Bolton and the Sefton and Liverpool regions.
- We find the growth rate to be slightly lower using these estimates in regions which have had mixed growth than presented in figure 5

Growth rate estimation: alternate method 2: To estimate growth rates we adapt a generalised additive model (GAM) where $I \propto \exp(s(t))$ for some smoother s(t). We use a quasi-Poisson family with canonical link and a thin-plate spline as implemented in the R package mgcv. The instantaneous local growth rate is then the time derivative of the smoother. The GAM can lead to boundary effects from the choice of smoother, so the most recent central estimates may not be reliable. Using this method, day-of-week effects can be considered. However we chose not to consider them here due to the very low case numbers each day, which resulted in day-of-week effects not improving the model fit. In Figure A3a we plot the temporal trends in the growth rate of symptomatic S+ individuals in each of the regions of concern, England, and England excluding the regions of concern. In Figure A3b we plot the corresponding fitted GAM and compare this to the data, in order to check the model performance.

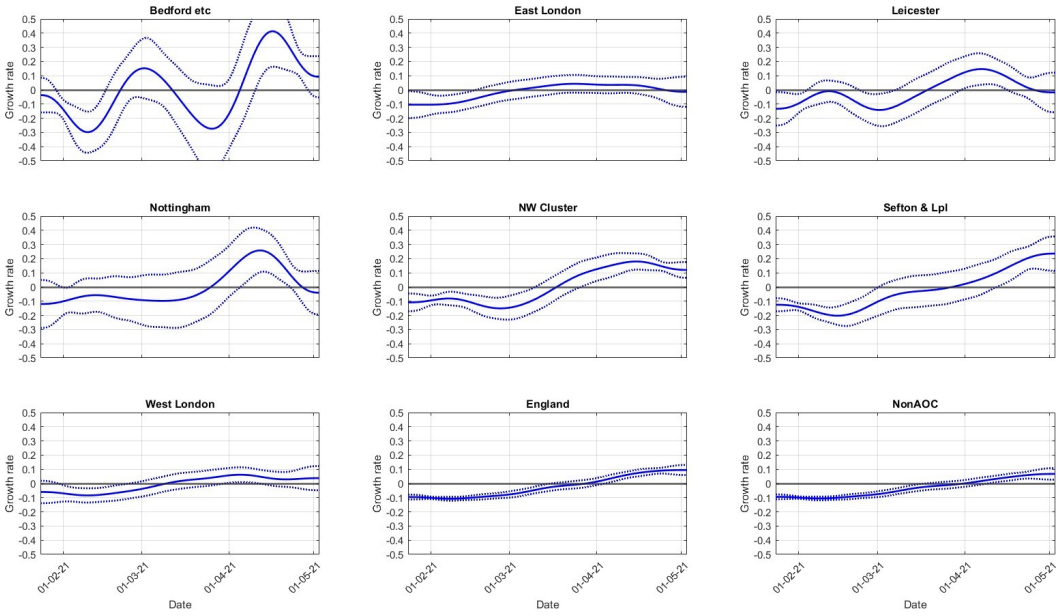


Figure A3a - Growth rate estimates in the symptomatic S+ data.

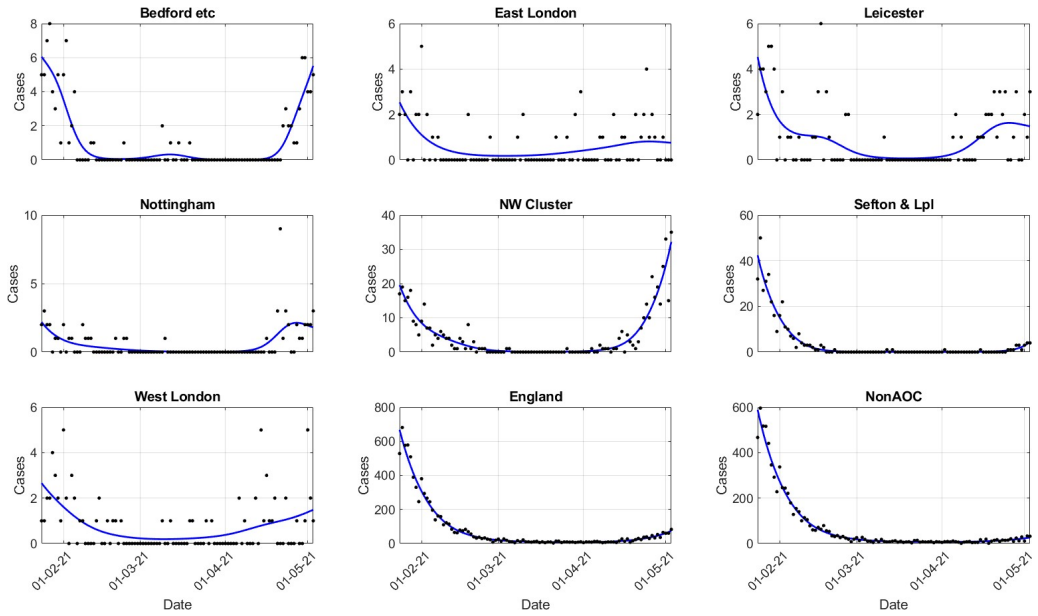
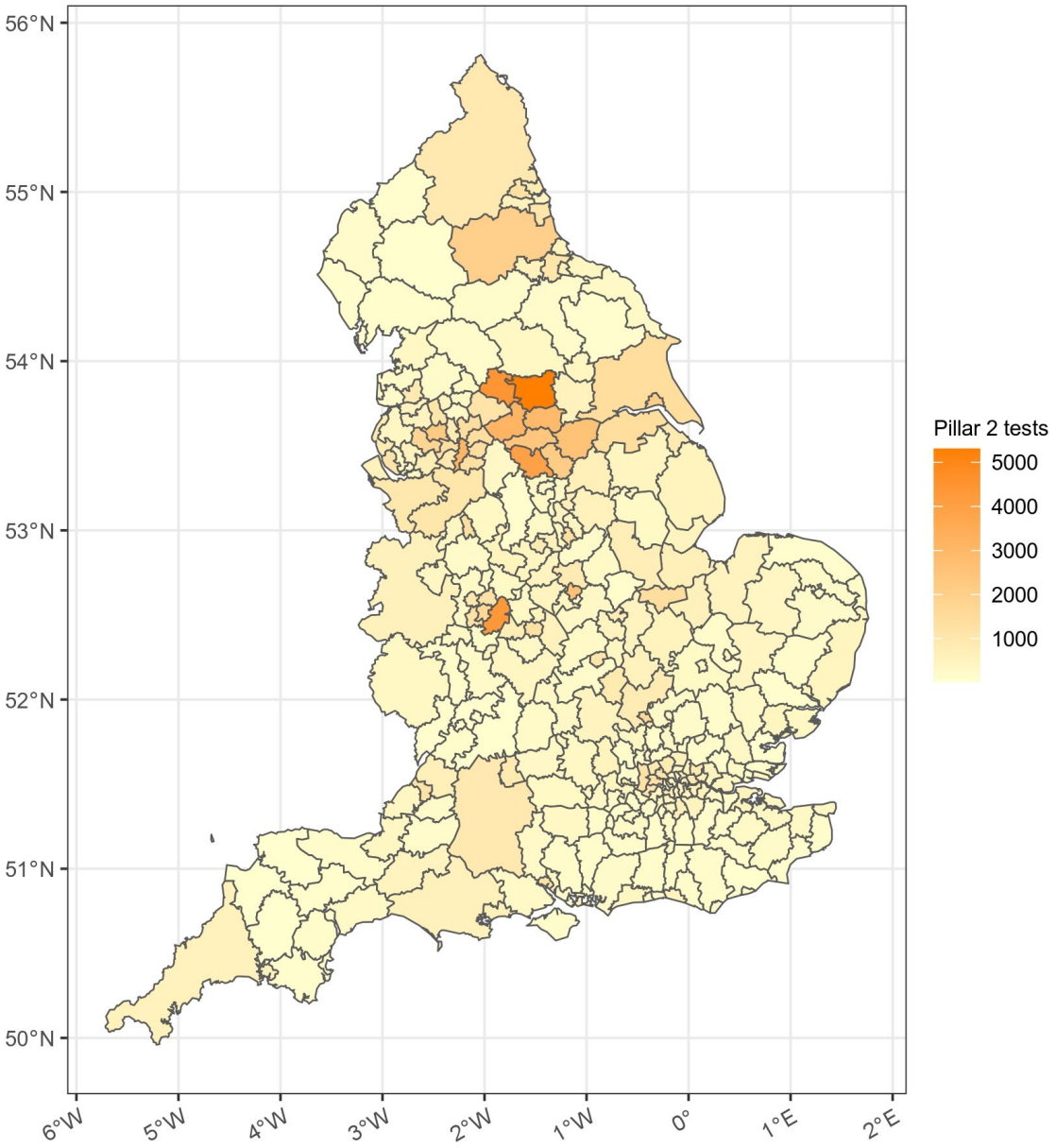


Figure A3b - Corresponding model fits to the symptomatic S+ data.

S-gene TaqPath test coverage

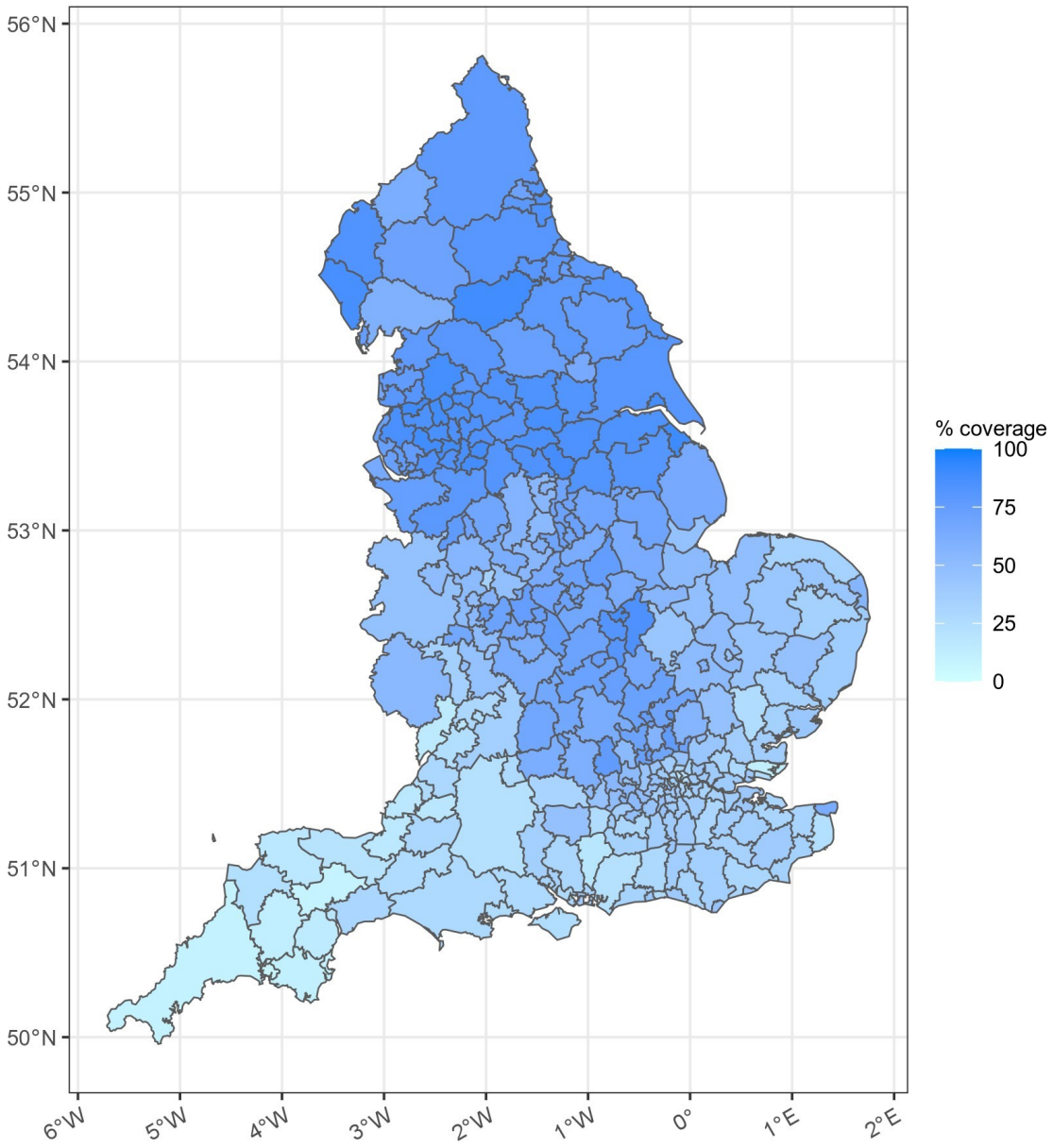
The degree of testing using the TaqPath assay varies from lab to lab. Since 1st March 2021 coverage of the S-gene test has been more extensive in the regions which we identify as problematic. This may be the result of an acquisition bias.

Since 1st March 2021 the number of pillar 2 positive cases varies substantially from region to region reflecting areas where the epidemic has taken more time to die down.



Supp Fig A4a - Pillar 2 positive cases by LTLA: 1st March 2021 - 8th May 2021.

The proportion of tests that are performed using the TaqPath testing system and therefore for which we will have S-gene results generally covers those areas which have had a lot of Pillar 2 testing, however regions with low case numbers also tend to have low TaqPath coverage and we must regard the S-gene signal in these areas as unreliable. Overall the TaqPath coverage in London for example is only about 50%.

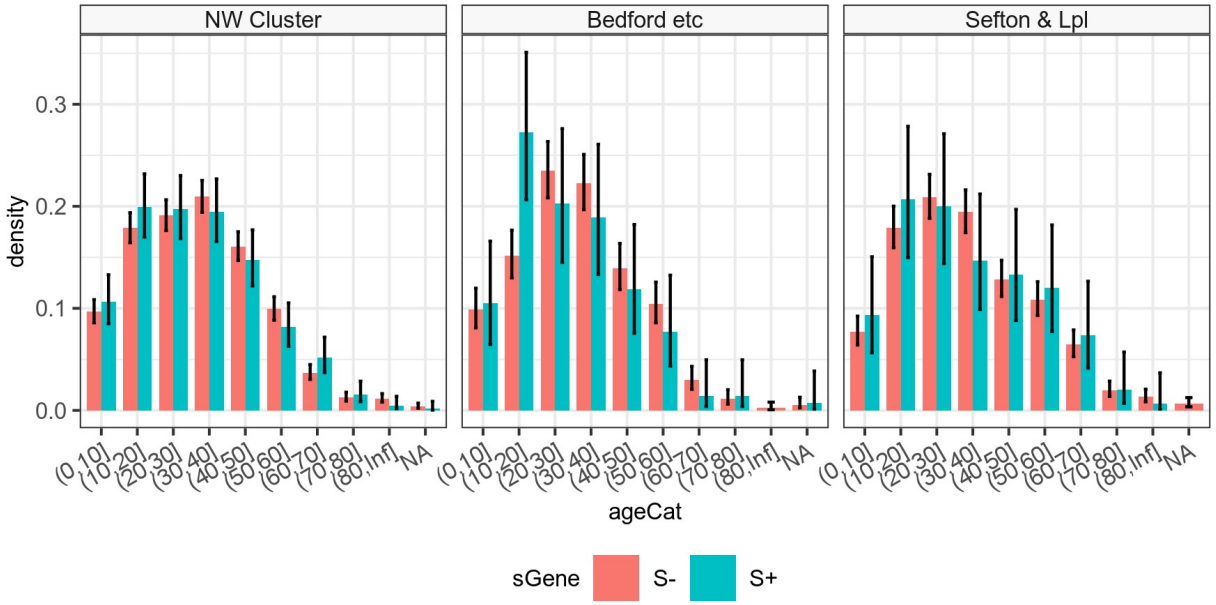


Supp Fig A4b - TaqPath test coverage by LTLA: 1st March 2021 - 8th May 2021.

Note added for release: Patterns of Taqpath coverage can change over time. If restricted to a shorter, more recent time period, Taqpath coverage appears to be more heterogenous than shown here - as seen in figure 13 of the PHE Technical Briefing 11 on SARS-CoV-2 variants of concern and variants under investigation in England.

Age distributions of clusters

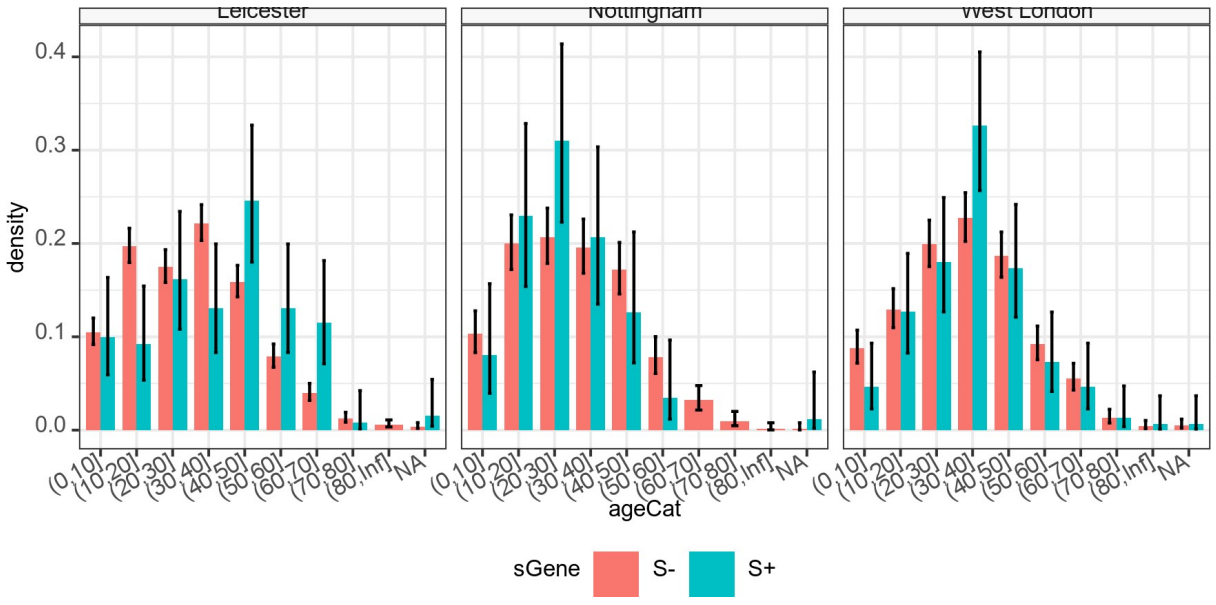
A) Putative community transmission regions. B.1.617.2 dominant



Supp Fig A5a - Age distribution of S+ and S- cases: 1st March 2021 - 8th May 2021.

- Generally ages consistent between two groups
- Except for increased S+ in 10-20 y.o. This could be a school outbreak in Bedford

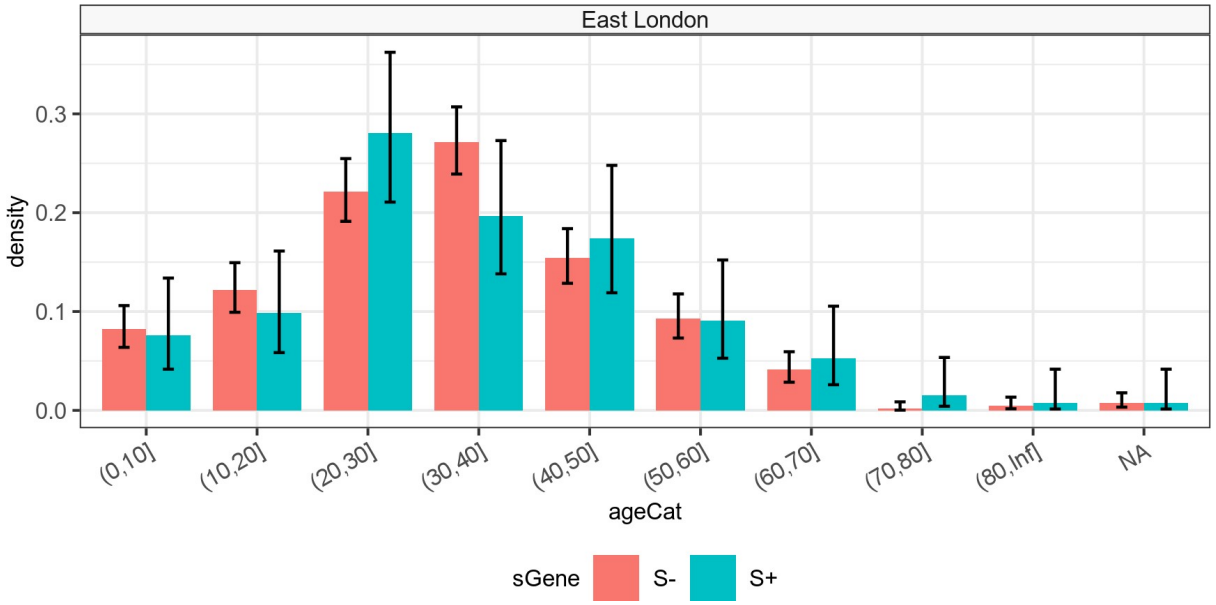
B) Mixed lineage with community / importation regions



Supp Fig A5b - Age distribution of S+ and S- cases: 1st March 2021 - 8th May 2021.

- Complex patterns varying between regions
- Older cases dominate in Leicester, unclear what significance of this is and needs further investigation.

C) B.1.351 dominant region



Supp Fig A5c - Age distribution of S+ and S- cases: 1st March 2021 - 8th May 2021.

- No significant age differences in this area.

Spatiotemporal model estimate

We are constructing a spatio-temporal IMLA model of sequenced variant types and S+ cases across the whole of England. This model can generate expected numbers of each individual variant in the model. This can be used to determine an estimate of per strain growth rate across England, by aggregating expected cases across space. The per strain growth rate estimated is as below. At the moment we are working on the uncertainty associated with these estimates