Local area reproduction numbers and S-gene target failure

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Abstract

Background: Local estimates of the time-varying effective reproduction number (Rt) of Covid-19 in England have become increasingly heterogeneous since the introduction of the November national lockdown in England. This variation may be attributed to the spread of a novel Covid-19 variant. In this report we aimed to investigate the changes in the proportion of positive cases that were S-gene negative ("S-gene target failure," SGTF), an indicator of the novel variant, and to correlate them with changes in the estimated reproduction number at the level of upper tier local authorities (UTLA).

Method: We explored the relationship between the proportion of samples that were S-gene negative and the effective reproduction number of test positive cases over time. Effective reproduction numbers were estimated using the `EpiNow2` R package independently for each local authority using two different estimates of the generation time. The `brms` R package was used to fit a range of regression models to estimate a multiplicative relationship between SGTF and weekly mean R. Models were compared using the expected log-predictive density.

Results: We found evidence of an association between increased mean Rt and the proportion of SGTF across all models evaluated with the magnitude of the effect increasing as model flexibility was decreased. Models found an effect consistent with the low ends of estimates that reported elsewhere when a generation time with a mean of 5.5 days was used. Models that adjusted for either national level or NHS region level residual variation over time were found to fit the data better and found yielded consistent results of the association of Rt with SGTF.

Conclusions: Our results indicate that even after adjusting for between NHS region residual variation over time S-gene negativity was associated with an increase in the effective reproduction number of Covid-19. These findings were robust across a range of models and generation time assumptions though the specific effect size was variable depending on the assumptions used. The lower bound of the estimated effect indicated that NPI measures implemented between September and January 1st in England may not be sufficient to reduce the reproduction number below 1.

Method

Data

We used 4 main sources of data: test positive Covid-19 notifications by UTLA,[1] S-gene status from PCR tests by local authority (Fig. 1) provided by Public Health England (PHE)[2], Google mobility data stratified by context,[3] and two publicly available data bases of of non-pharmaceutical interventions by UTLA.[5] We aggregated the data at the weekly level and restricted the analysis to the period beginning Monday, 5 October.

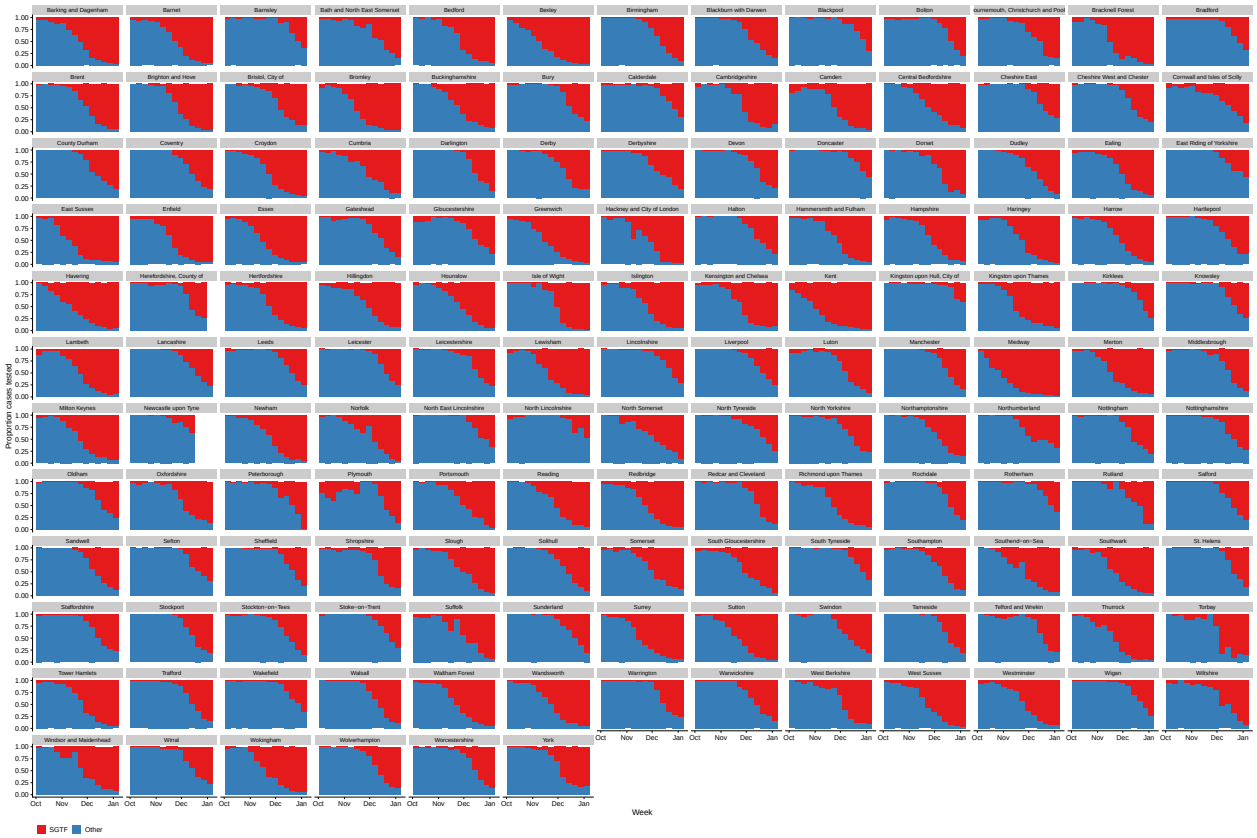

Figure 1: Proportion of test-positives that had a S-gene result reported which was S-gene positive/negative by LTLA and week of infection (assumed one week before test).

Statistical analysis

We calculated the weekly proportion of positive tests that were S-gene negative over time by local authority. We estimated reproduction numbers using the method described in[6] and[7] and implemented in the `EpiNow2` R package.[8] Daily updated estimates can be downloaded at https://github.com/epiforecasts/covid-rt-estimates/blob/master/subnational/united-kingdom-local/cases/summary/rt.csv. We used two sets of estimates, obtained using uncertain, gamma distributed, generation interval distributions with a mean of 3.6 days (standard deviation (SD): 0.7), and SD of 3.1 days (SD: 0.8)[8,9] or with a mean of 5.5 days (SD: 0.5 days), and SD of 2.1 days (SD: 0.25 days),[10] respectively.

We then built a separate model of the expected reproduction number in UTLA i during week t starting in the week beginning 14 September, 2020, as a function of local restrictions, mobility indicators, residual temporal variation, and proportion of positive tests S-gene negative:

$$R_{i,t} = (1 + \alpha f_{it}) \exp\left(s(t) + \sum_j \beta_j T_{ijt} + \sum_k \gamma_k G_{ikt} + \log R_i \right)$$

where R_t is an UTLA-level intercept corresponding to Rt during national lockdown in November, T_{ijt} is 1 if intervention j (out of: no tiers, tier 1/2/3) is in place and 0 otherwise, G_{ikt} is the relative mobility in context k (home, parks, workplace, etc.) at time t in UTLA i as measured by Google, and $s(t)$ is a time-varying component, modelled either as a region-specific thin-plate regression spline ("Regional time-varying"), the sum of a static regional parameter and a national spline ("National time-varying"), or only a static regional parameter ("Regional static"). The key parameter is α, the relative change in reproduction number in the presence of the SGTF that is not explained by any of the other variables, where f_{it} is the proportion out of all positive tests for SARS-CoV-2 where the S-gene was tested with SGTF, and the reproduction number in

any given UTLA is

$$R_{t,i} = (1 - f_{it})R^{+}_{t,i} + f_{it}R^{-}_{t,i}$$

where $R^{-}_{t,i}$ is the S-gene negative reproduction number, $R^{+}_{t,i}$ is the S-gene positive reproduction number, and it is assumed that $R^{-}_{t,i} = (1 + \alpha)R^{+}_{t,i}$

We used a Student's t-distribution observation model with a single variance parameter and a single degrees of freedom parameter. All models were implemented using the `brms`[12] package in `R`. All code required to reproduce this analysis is available from https://github.com/epiforecasts/covid19.sgene.utla.rt/.

Results

We found consistent evidence of an association between S-gene negativity and increased UTLA level reproduction number estimates. The association became more apparent over time from the middle of October through to the beginning of December (Fig. 2) as the proportion of of tests that were S-gene negative increased heterogeneously across NHS regions. The association appeared to be both across NHS regions and within NHS regions. Models that adjusted for residual variation over time on both a national and NHS region level fit the data better than those that did not (Table 1) but all models had evidence of increased Rt with S-gene negativity with the best fitting model yielding a lower bound of 16% higher Rt of SGTF cases with a short generation time (Table 2), slightly higher than the model that only adjusted for national level residual variation over time (lower bound: 22%) and lower than the model that did not adjust for residual variation over time (lower bound: 56%). With a longer generation time, these lower bounds changed to 22%, 36%, and 56%, respectively. The upper bound of the increase in Rt varied from % to 65% in models that fit the data comparably (but had different assumed generation times).

The best fitting model appeared to reproduce estimated reproduction numbers well over time (Fig. 3) although there are notable outliers in some of the weeks. Alternative model parametrisations fit the data less well than those presented here whilst producing comparable effect size estimates.

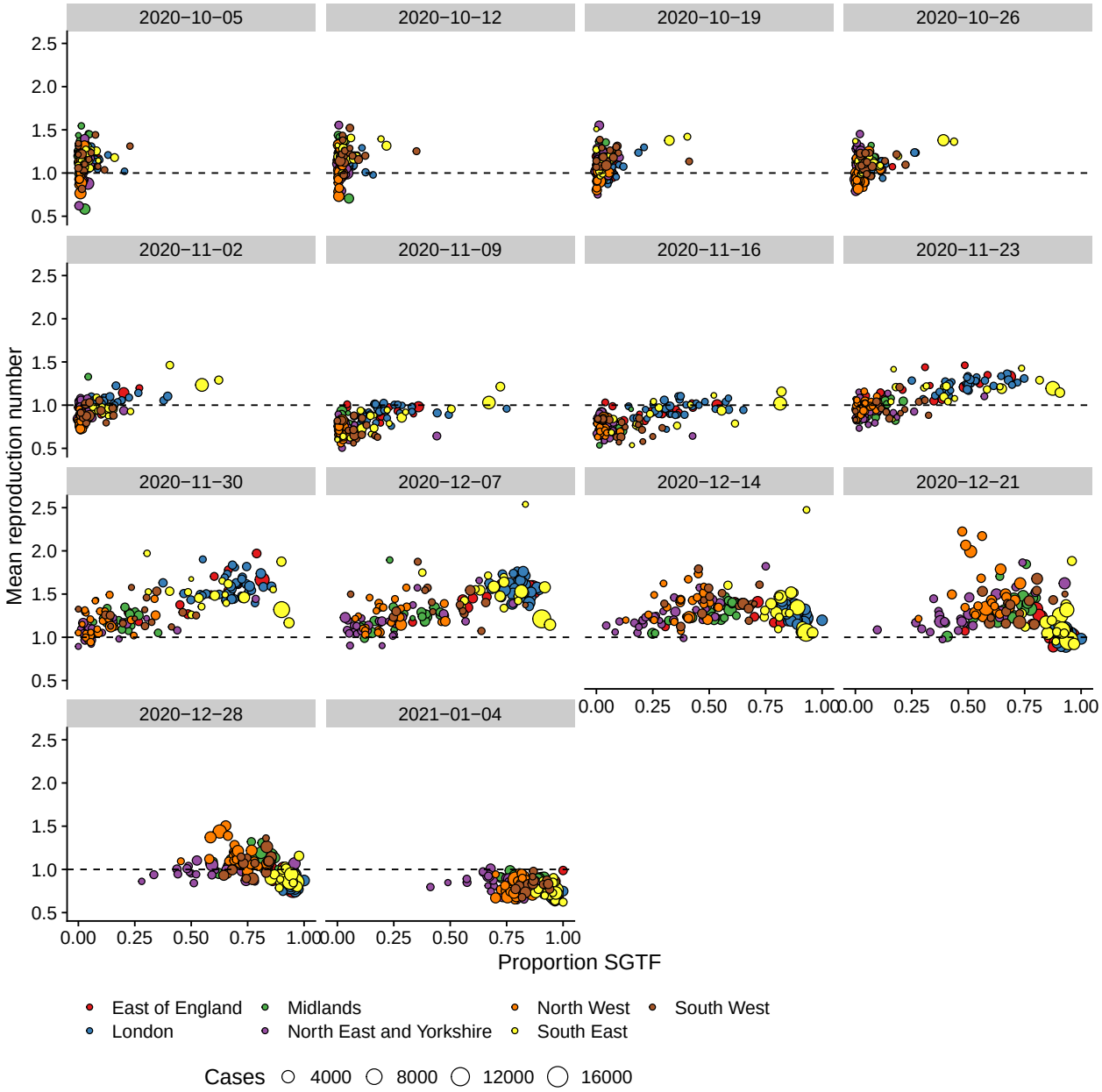

Figure 2: Mean reproduction numbers using a generation time with a mean of 5.5 days since the week beginning 14 September, 2020, compared to the proportion of all test-positives tested for S-gene that tested S-gene positive/negative that week. Each point represents one UTLA, with the size given by the number of cases in the week following the week of the given reproduction number to account for the delay from infection to testing.

Model	ELPD difference
Regional time-varying	0.00
National time-varying	-303.10
Regional static	-575.14

Table 1: Model comparison (long generation interval) by difference in expected log-predictive density.

Model	Estimate (short GT)	Estimate (long GT)
Regional static	0.4 (0.37-0.43)	0.61 (0.56-0.65)
National time-varying	0.26 (0.22-0.3)	0.41 (0.36-0.46)
Regional time-varying	0.19 (0.16-0.21)	0.26 (0.22-0.3)

Table 2: Parameter α with 95% credible intervals for the three different models of $s(t)$ for short (3.6 days mean) and long (5.5 days mean) generation intervals. The estimate corresponds to the multiplicative increase in reproduction number estimated for S-gene negative cases.

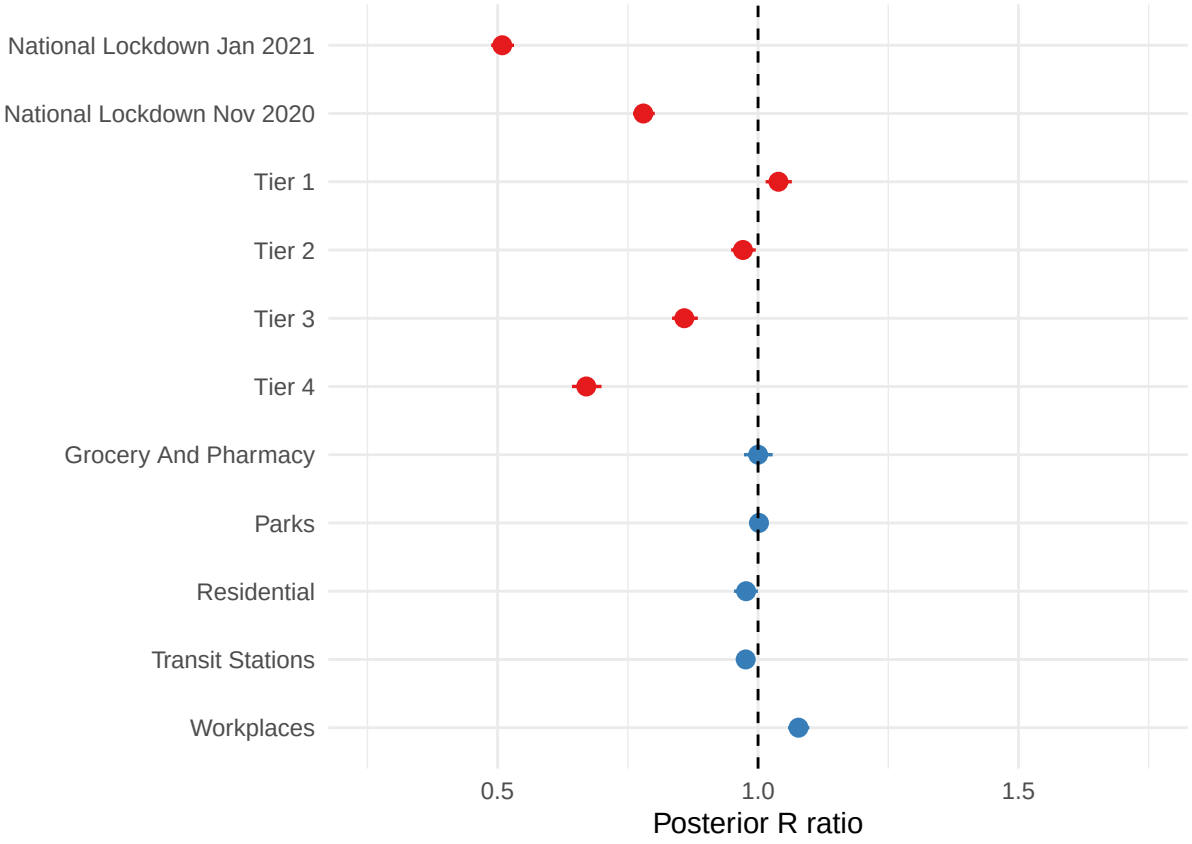

Figure 3: Parameter estimates (R ratios) of the Regional static model. These correspond to a multiplicative effect on a baseline R=1 (95% CI: 1.01–1.07). Intervention indicators are coloured in red, and mobility indicators in blue

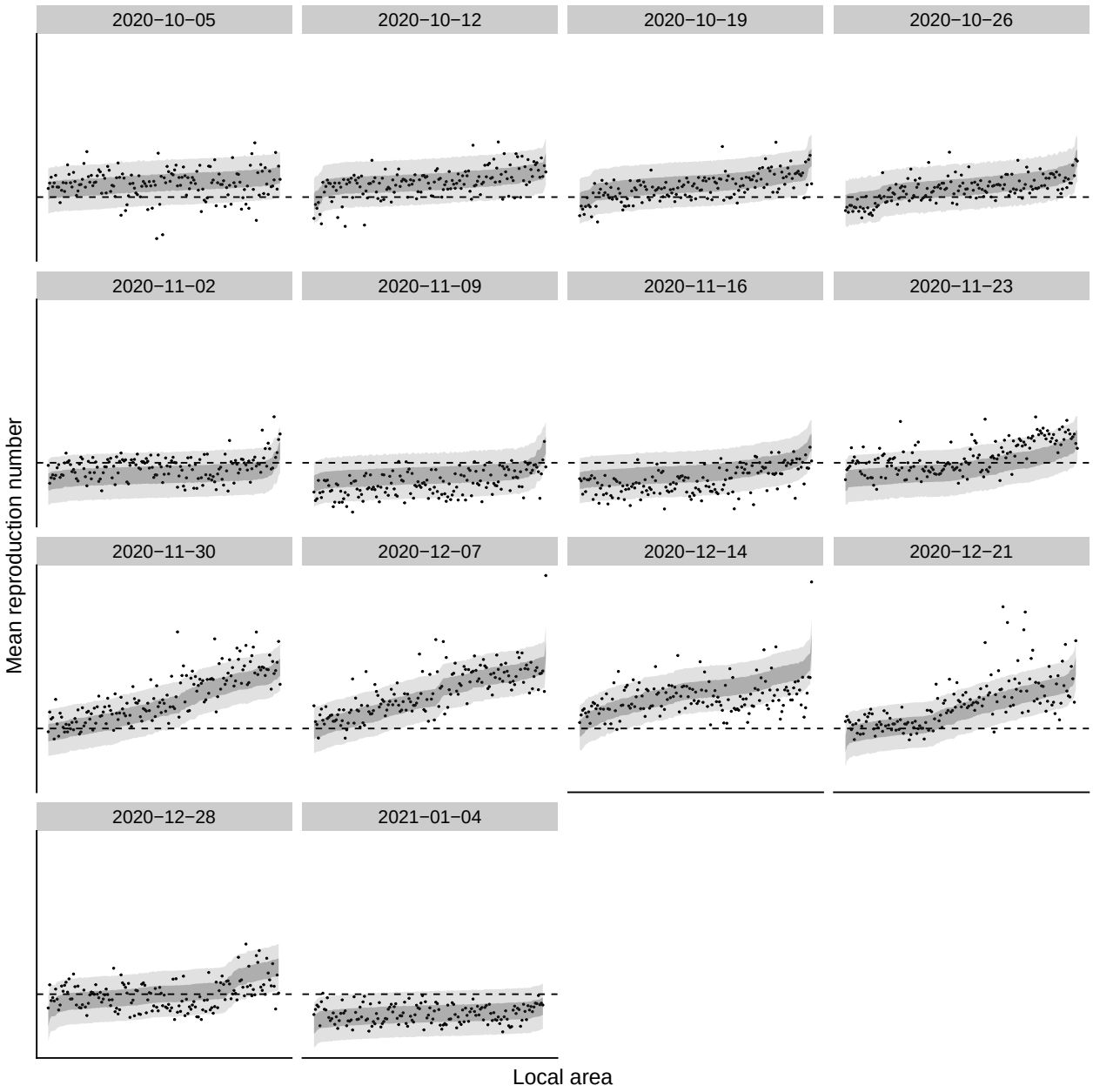

Figure 3: Predictions of the regional static model with long generation interval (per-region spline) compared to the data (solid dots). Dark grey: central 50% prediction interval; light grey: central 90% prediction interval. Areas are ordered each week according to predicted median.

Discussion

We studied the relationship between SGTF (as a proxy for the new variant of concern) and the effective reproduction number using three related models that had varying degrees of flexibility in ascribing changes in the effective reproduction number to factors not explained by the proportion of cases with SGTF. The modelled that associated all temporal variation with interventions, mobility and SGTF produced the largest increases (central estimates: 61% and 40% increase with long and short generation interval, respectively). A more conservative model with region-specific splines yielded central estimates of a 19% and 26% increase in R with short and long generation interval, respectively. While this model yielded the best fit to the data the estimate of increased R associated with SGTF may well be an underestimate as it can explain regional

differences by unmodelled factors, i.e. ones beyond interventions, mobility, and distribution of SGTF, and is therefore largely a model of within-regions UTLA-level differences. On the other hand, the fact that this model yielded a better fit than the model without splines suggests that that model is affected by confounders not included in the model.

Our estimates with the longer generation interval without adjusting for additional residual variation over time are consistent with ones from two other modelling studies using similar generation intervals (5.5 and 6.5 days, respectively), which were in the order of a 50-74%[13] or 50-75%[14] increase. Shorter generation intervals lead to reproduction numbers closer to 1 and thus possibly lower estimates of a multiplicative effect. This may be a particular issue where the effect of the variant would cause the reproduction number to cross 1.

Our results should be treated with caution as several caveats apply: we have not observed any local authorities in which all tests were S-gene negative and therefore are extrapolating beyond the available data. We assumed that S-gene positive and negative cases had the same generation interval, while a complementary hypothesis might be that the new variant shortened the generation interval. We assumed that the effect of tiers and lockdown applied uniformly across the country. While we did allow for a flexible regional-level behaviour through our use of regression splines, there may be UTLA level variation that we did not capture in doing so. If this could explain some of the sub-regional differences in reproduction numbers, our estimate for the increased reproduction number could biased. Lastly, we fitted the model only to the mean estimated reproduction numbers and therefore ignored uncertainty in these estimates as well as in the proportion of SGTF observed in every UTLA per week. Because of this, uncertainty in our regression coefficients are underestimated, and probably considerably so. Lastly, SGTF does sometimes occur with other variants and we therefore cannot rule out that our effect includes a component not related to the new variant. Further investigation will be necessary in order to establish the relationship between SGTF and the reproduction number.

We found consistent evidence that SGTF was associated with increased reproduction numbers across a range of models and assumptions. The precise estimate of the effect size was impacted by the both the degree of flexibility allowed in the model used and the assumed generation time. However, the lower bound of the effect implies that NPI measures implemented since September in England may not be sufficient to reduce the reproduction number below 1. Our analysis is fully reproducible and all the aggregated data used is publicly available for reuse and reinterpretation.

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