Population-level association between S-gene target failure and the relationship between cases, hospitalisations and deaths of Covid-19

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Aim

Explore the association between S-gene target failure and the relationship between test-positive cases, Covid-19 hospitalisations and Covid-19 deaths by NHS region and Upper-tier Local Authority (UTLA) at the population level.

Method

Data

We used 4 main sources of data: test positive Covid-19 notifications by UTLA,[1] hospitalisations with Covid-19 by UTLA,[2] deaths linked to Covid-19 notification within 28 days of notification,[1] and S-gene status from PCR tests by local authority provided by Public Health England (PHE)[3]. We aggregated the data at the weekly level and restricted the analysis to the period beginning Monday, 5 October.

Statistical analysis

We calculated the weekly proportion of positive tests that were S-gene negative over time by local authority and adjusted to date of infection from date of specimen by shifting all estimates back by a week. We estimated pairwise fixed lags between cases, admissions and deaths by maximising Pearson's correlation coefficient. We aggregated all data by week of infection.

We assumed that the observed number of Covid-19 admissions/deaths ($D_{i,t}$) within 28 days by date of infection were a function of Covid-19 notifications/admissions ($C_{i,t}$) by date of infection scaled by the case fatality rate of S-gene positive cases (c^+) and S-gene negative cases (c^-),

$$D_{i,t} \sim \text{NB}\left(c^+ \left(1 - f_{it}\right) C_{i,t} + c^- f_{it} C_{i,t}, \phi\right)$$

where i indicates UTLA, t week of infection, and f_{it} is the fraction of cases that were found to be S-gene negative by UTLA each week. The case fatality rate (or hospitalisation-fatality rate / case-hospitalisation rate, respectively) of S-gene negative cases then assumed was then assumed to be a function of static local variation, normalised Covid-19 notifications by date of infection, and residual temporal variation.

$$c^+ = \text{logit}^{-1}\left(\gamma_{i,t}\right)$$

where $\gamma_{i,t}$ is either a UTLA-level intercept $\gamma_{i,t} \equiv \delta_i$ corresponding to the baseline case fatality rate per UTLA, or a temporal intercept $\gamma_{i,t} \equiv \theta_t$ corresponding to the baseline case fatality rate over time, with each

time point treated as independent. In other words, we stratify the data set either by UTLA or by week and determine whether differences in the associations between cases, admissions and deaths are explained by changes in proportion of cases that are SGTF over time and space, respectively.

The S-gene negative case fatality rate was then assumed to be related to the S-gene positive case fatality rate via a multiplicative relationship,

$$c^- = \alpha c^+$$

or an additive relationship

$$c^- = \alpha + c^+$$

where α represents either the multiplicative change in case fatality rate or the additive change. These alternative parameterisations represent either a population wide effect for the former parameterisation or a subpopulation effect in the latter parameterisation.

All models were implemented using the `brms`[4] package in `R`. All code required to reproduce this analysis is available from https://github.com/epiforecasts/covid19.sgene.utla.rt/.

Results

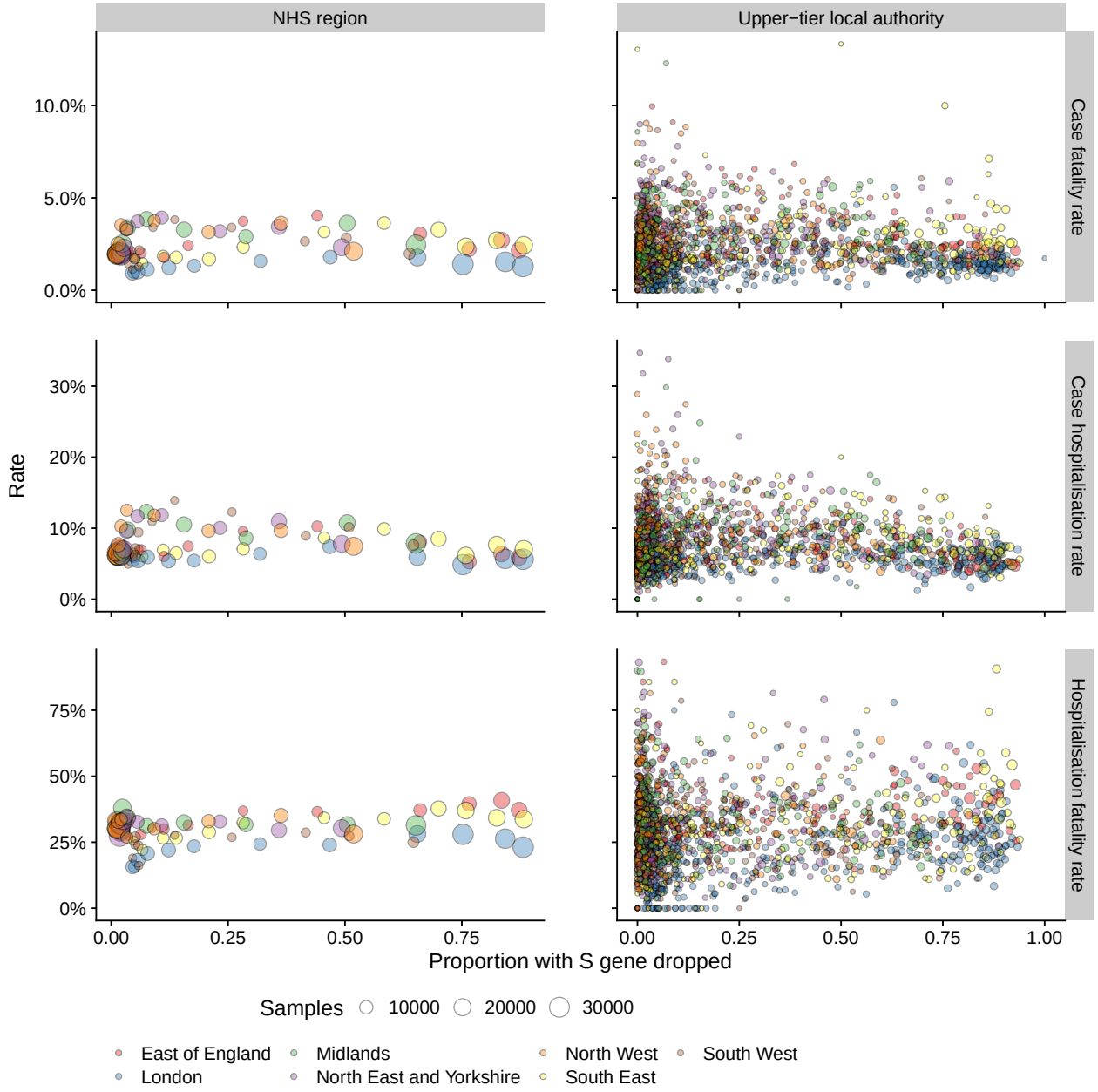

Figure 1: Proportion with S gene dropped compared to the adjusted severity rates each week beginning Monday the 5th of October by NHS region and upper-tier local authority (UTLA). Each point represents one NHS region or UTLA and one week, with the size of the point given by the number of PCR tests.

Table 1: Estimated unadjusted effect of S-gene negativity on severity rates (median with with 95% credible intervals) for the both additive and multiplicative assumptions across spatial aggregations and delay approaches considered. In additive models the effect can be interpreted as a direct change in the rate related to S-gene negativity whilst in multiplicative model the effect can be interpreted as a scaling of the S-gene positive rate.

Method	Aggregation	Effect type	Case fatality rate	Case hospitalisation rate	Hospitalisation fatality rate
Global lag	NHS region	Additive	0.0052 (-0.0014, 0.012)	0.0031 (-0.0086, 0.015)	0.0099 (-0.0075, 0.028)
Global lag	UTLA	Additive	0.0014 (-0.00095, 0.0038)	-0.0037 (-0.0091, 0.0022)	0.016 (0.00069, 0.03)
Global lag	NHS region	Multiplicative	1.2 (0.93, 1.7)	1.1 (0.83, 1.3)	1.2 (1, 1.4)
Global lag	UTLA	Multiplicative	1.1 (0.96, 1.2)	0.94 (0.87, 1)	1.1 (1, 1.2)
Global convolution	NHS region	Multiplicative	1.8 (1.5, 2)	1.2 (1, 1.4)	1.3 (1.1, 1.4)
Global convolution	UTLA	Multiplicative	1.1 (0.98, 1.1)	0.94 (0.89, 0.98)	1.2 (1.2, 1.3)
Local convolution	NHS region	Multiplicative	1.7 (1.5, 1.9)	1.4 (1.3, 1.6)	1.2 (1, 1.3)

Table 2: Estimated adjusted effect of S-gene negativity on severity rates (median with with 95% credible intervals) for the both additive and multiplicative assumptions across spatial aggregations and delay approaches considered. In additive models the effect can be interpreted as a direct change in the rate related to S-gene negativity whilst in multiplicative model the effect can be interpreted as a scaling of the S-gene positive rate. Effect estimates are adjusted for location variability and for current case/hospital admissions.

Method	Aggregation	Effect type	Case fatality rate	Case hospitalisation rate	Hospitalisation fatality rate
Global lag	NHS region	Additive	0.02 (0.016, 0.024)	0.041 (0.028, 0.051)	0.0075 (-0.011, 0.026)
Global lag	UTLA	Additive	0.014 (0.013, 0.016)	0.043 (0.04, 0.047)	0.048 (0.032, 0.063)
Global lag	NHS region	Multiplicative	2.7 (2.2, 3.3)	2.1 (1.8, 2.5)	1.1 (0.94, 1.3)
Global lag	UTLA	Multiplicative	2.4 (2.2, 2.6)	2.1 (1.9, 2.2)	1.4 (1.3, 1.5)
Global convolution	NHS region	Multiplicative	2.4 (2.1, 2.6)	1.6 (1.5, 1.8)	0.96 (0.84, 1.1)
Global convolution	UTLA	Multiplicative	2 (1.8, 2.1)	1.7 (1.6, 1.8)	1.2 (1.1, 1.3)
Local convolution	NHS region	Multiplicative	2.4 (2.1, 2.6)	1.6 (1.5, 1.8)	0.95 (0.84, 1.1)

Discussion

We studied the relationship between SGTF (as a proxy for the new variant of concern) and the association between Covid-19 cases, hospitalisations and deaths adjusted using both an additive and a multiplicative relationship. We considered space and time as confounders.

References

1. *Coronavirus (covid-19) in the uk.* (2021). https://coronavirus.data.gov.uk/details/healthcare.

2. Meakin, S., Abbott, S., & Funk, S. (2021). *NHS trust level covid-19 data aggregated to a range of spatial scales.* https://doi.org/10.5281/zenodo.4447465

3. England, P. H. (2020). *Investigation of novel sars-cov-2 variant: Variant of concern 202012/01.* https://www.gov.uk/government/publications/investigation-of-novel-sars-cov-2-variant-variant-of-concern-20201201.

4. Bürkner, P.-C. (2018). Advanced Bayesian multilevel modeling with the R package brms. *The R Journal*, *10*(1), 395–411. https://doi.org/10.32614/RJ-2018-017

Appendix: fits