Increased hazard of mortality in cases compatible with SARS-CoV-2 variant of concern 202012/1 - a retrospective case-control study

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Summary

- We perform a matched case-control study of Pillar 2 data, matching S gene positive and S gene negative cases on age, specimen time, location, ethnicity, gender and index of multiple deprivation. This controls for many potential biases including limitations in hospital capacity.
- We find that the mortality hazard ratio of the variant of concern (VOC202012/1) is 1.91 (1.35 - 2.71) in patients who have tested positive for COVID-19 in Pillar 2.
- The group studied includes middle age and late middle aged adults in whom death is less common.
- Care must be taken in generalising the conclusions of this analysis to other population groups, in particular the elderly in hospital, as we had no information about the variant of concern in these groups.
- The increased hazard rate could be partially explained by changes in test-seeking behaviour if there are significant changes in symptomatology of the variant of concern.
- At face value, combined with the increased transmission rate, the new variant has the potential to cause substantial additional mortality over and above current projections.

Background

A variant of concern of the SARS-CoV-2 virus (VOC-202012/1, variant B.1.1.7 - 'new variant') has been identified in the UK. It spread rapidly in London, the East and the South East of England, and has since spread throughout the UK.

When tested using the taqPath system it has been shown that there is a close correlation between VOC cases confirmed by sequencing and the failure of detection of the S gene, as compared to the N gene and ORF1ab gene. S gene negative cases have been used to track the progression of the new variant.

Methods

We selected tests results performed by Pillar 2 lighthouse labs for people that had a single positive PCR test using the taqPath assay and for which we had PCR cycle threshold (CT) values for the S, N and ORF1ab components of SARS-CoV-2.

We classified the results as S+N+ORF+ ("S gene positive") for results that had the following CT values: S gene < 40; N gene < 30; ORF1ab gene < 30. We classified S-N+ORF+ ("S gene negative") for results that had CT values: S gene not detected; N gene < 30; ORF1ab gene < 30. All other results were classified as "Equivocal." We differentiated between S gene negative cases prior to 1st October 2020, and the proposed emergence of VOC-202012/01, as "S gene negative pre B.1.1.7", "S gene negative post B.1.1.7".

We matched to the line list of case details and line list of details of death (if present) using a unique study identifier. Many cases, for example from Pillar 1 testing were not conducted using the taqPath system and the S gene status is "Unknown". We analysed this full data set for systematic biases based on the 5 categories of "S gene positive", "S gene negative pre B.1.1.7", "S gene negative post B.1.1.7", "Equivocal" and "Unknown" which we summarise in our supplementary material.

Significant systematic biases exist in the full data set that influence the interpretation of comparative analyses. To address those, we designed and performed a retrospective case-control study. From the full data set we selected Pillar 2 cases since 1st Oct 2020 with S gene positive (S+N+ORF+) or S gene negative (S-N+ORF+) results. We paired S gene positive and S gene negative cases by matching on gender, ethnicity, index of multiple deprivation, location (as lower tier local authority region), age (within a tolerance of <2 years), and date of positive specimen (within a tolerance of <4 days). Before pairing we excluded all cases less than 30 years of age as they did not contribute to the mortality data.

We compared the rates of death within 28 days of a positive COVID test in Pillar 2 data between cases found to be S gene positive versus S gene negative cases. We calculated the hazard ratio of death given a S gene negative test result, versus death given a S gene positive test result using a Cox proportional hazards model, taking into account censoring.

Results

We identified 66,208 matching pairs of patients with similar age and specimen date, and identical gender, ethnicity, geography, and index of multiple deprivation. Of these 132,416 patients, 143 died within 28 days of a positive test (0.1%) - see Table 1. The matching process is observed to control well for all demographic variables, and geographic variables (with slight mismatches due to differences in scale from matching and reporting). With age and specimen date, where we allowed small tolerances, the average difference between ages in the S gene positive and S gene negative arms was 0.0 years and a mean difference of 0.2 days for specimen date (with S negative specimens taken later than S positives).

Table 1 - S gene positive (control) & S gene negative matched case controls based on age, ethnicity, gender, index of multiple deprivation, geography and specimen date (not shown). For comparison the subset of patients from both arms who died are presented in the right 3 columns.

category	value	S pos N	S pos %age	S pos mean (SD)	S neg N	S neg %age	S neg mean (SD)	Died N	Died %age	Died mean (SD)
Age		66208		45.5 (±10.6)	66208		45.5 (±10.6)	143		62.7 (±13.3)
Age by category	30-59	59553	89.9%		59553	89.9%		58	40.6%	
	60-69	5421	8.2%		5421	8.2%		35	24.5%	
	70-79	1069	1.6%		1069	1.6%		36	25.2%	
	80+	165	0.2%		165	0.2%		14	9.8%	
Ethnicity	White	53574	80.9%		53574	80.9%		119	83.2%	
	Asian	10396	15.7%		10396	15.7%		24	16.8%	
	Other	1131	1.7%		1131	1.7%				
	Afro-carribbean	1107	1.7%		1107	1.7%				
Gender	Female	35539	53.7%		35539	53.7%		56	39.2%	
	Male	30669	46.3%		30669	46.3%		87	60.8%	
IMD	1	5563	8.4%		5563	8.4%		11	7.7%	
	2	12949	19.6%		12949	19.6%		25	17.5%	
	3	9541	14.4%		9541	14.4%		22	15.4%	
	4	7875	11.9%		7875	11.9%		11	7.7%	
	5	6202	9.4%		6202	9.4%		23	16.1%	
	6	4549	6.9%		4549	6.9%		12	8.4%	
	7	4589	6.9%		4589	6.9%		11	7.7%	
	8	4733	7.1%		4733	7.1%		10	7.0%	
	9	4907	7.4%		4907	7.4%		8	5.6%	
	10	5300	8.0%		5300	8.0%		10	7.0%	
N gene CT		66208		21.4 (±4.2)	66208		18.9 (±4.4)	143		18.6 (±4.1)
Region	East of England	4958	7.5%		4964	7.5%		10	7.0%	
	London	12744	19.2%		12744	19.2%		17	11.9%	
	Midlands	14548	22.0%		14554	22.0%		30	21.0%	
	North East and Yorkshire	10523	15.9%		10527	15.9%		23	16.1%	
	North West	16303	24.6%		16293	24.6%		41	28.7%	
	South East	6086	9.2%		6080	9.2%		19	13.3%	
	South West	1046	1.6%		1046	1.6%		3	2.1%	
S gene	Positive	66208	100.0%					49	34.3%	
	Neg Post B.1.1.7				66208	100.0%		94	65.7%	
Status	Dead <28 days	49	0.1%		94	0.1%		143	100.0%	
	Other	66159	99.9%		66114	99.9%				

Compared to cases we observe a greater proportion of deaths in older age groups (mean 62.7 years old versus 45.5 years old), and in men, as has been seen in previous work. We note both

cases and deaths are under-represented in the South West and East of England where the Pillar 2 labs have not used taqPath assays until recently.

We found 94 deaths in the S negative arm of the study compared to 49 in the S positive arm. This gives a hazard ratio of 1.91 (95% confidence intervals 1.35 - 2.71; $p < 0.001$) see table 2.

Table 2 - Hazard ratios for death given an S gene negative test result versus deaths given a S gene positive result (reference category). Hazard ratios greater than one are indicative of an increased rate of death due in infections compatible with VOC202012/01. In model 1 we look at only the S gene status as an indicator, in model 2 we include variability in the N gene CT value measured on original specimen as a continuous predictor, which explains some but not all of the hazard increase observed due to S gene negativity.

Model	Variable	Beta (SE)	HR (95% CI)	P
1) S Gene only	sGene			
	— Positive (ref)	–	–	–
	— Negative	0.65 (0.18)	1.91 (1.35, 2.71)	<0.001
2) S Gene + N Gene CT	sGene			
	— Positive (ref)	–	–	–
	— Negative	0.50 (0.18)	1.65 (1.15, 2.36)	0.006
	CT_N	-0.06 (0.02)	0.94 (0.90, 0.98)	0.002

The case matching design controls for most potential biases including variations in hospital capacity, as it pairs patients by demographics, geography and time of testing. We investigated other further potential biases that may be present. There is no evidence for asymmetric delays in time from test to admission shown in figure 1 panel A.

It is noted in table 1 and in figure 1 panel B that CT values for the N gene are lower in S gene negative cases than in S gene positive cases and this effect is potentiated in those who died. Low values for N gene cycle threshold imply the viral load in patients at the time of sampling were higher. This could be regarded as a source of bias or as a feature of S gene negative infection. If we interpret it as a source of bias, we can control for N gene CT value in the Cox proportional hazards model (in table 2 - model 2) which shows a reduction in the overall hazard of S gene negativity to 1.65, but which remains significantly above 1.

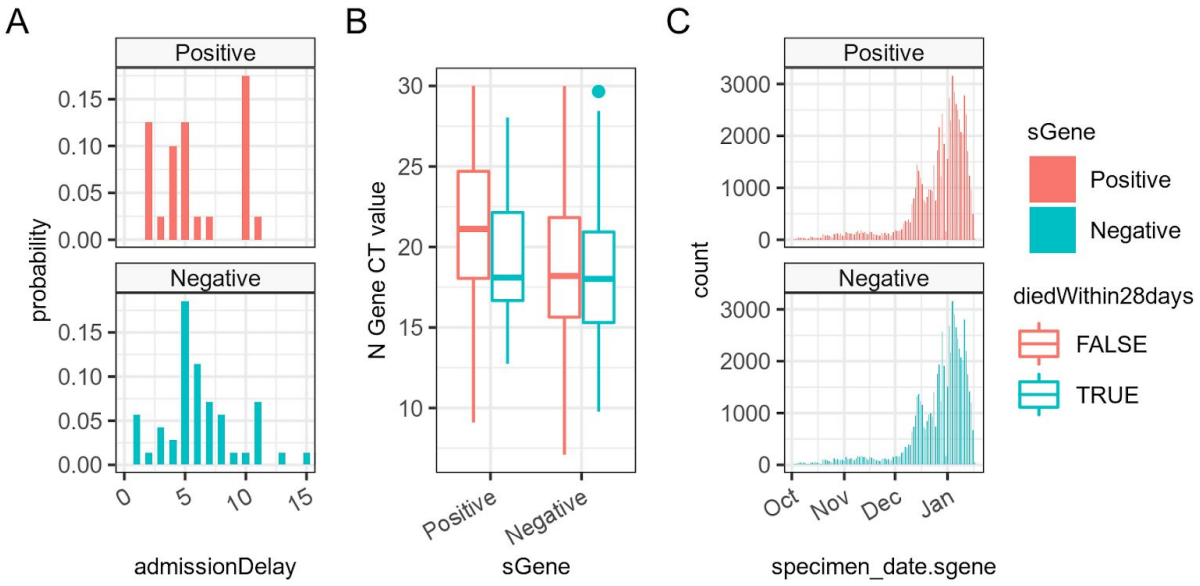


Figure 1 - Investigation of biases in the case control arms. In panel A we see delays between specimen and admission in patients who subsequently died. In panel B we see median CT values for the N gene for both S gene positive and negative cases. In panel C we see the date distribution of the specimens in our matched pairs of S gene positive and negative cases.

Limitations

The increase in hazard of death is observed in S gene positive infections detected in Pillar 2 testing, versus S gene negative infections detected in Pillar 2. Pillar 2 testing covers a younger age group who are in the community and hence at least initially less severe than cases detected through Pillar 1. In Pillar 2 cases, death is a comparatively rare outcome, compared to in-hospital identified cases. We do not have information about the S gene status of patients in hospital, which is the group of patients with the greatest mortality.

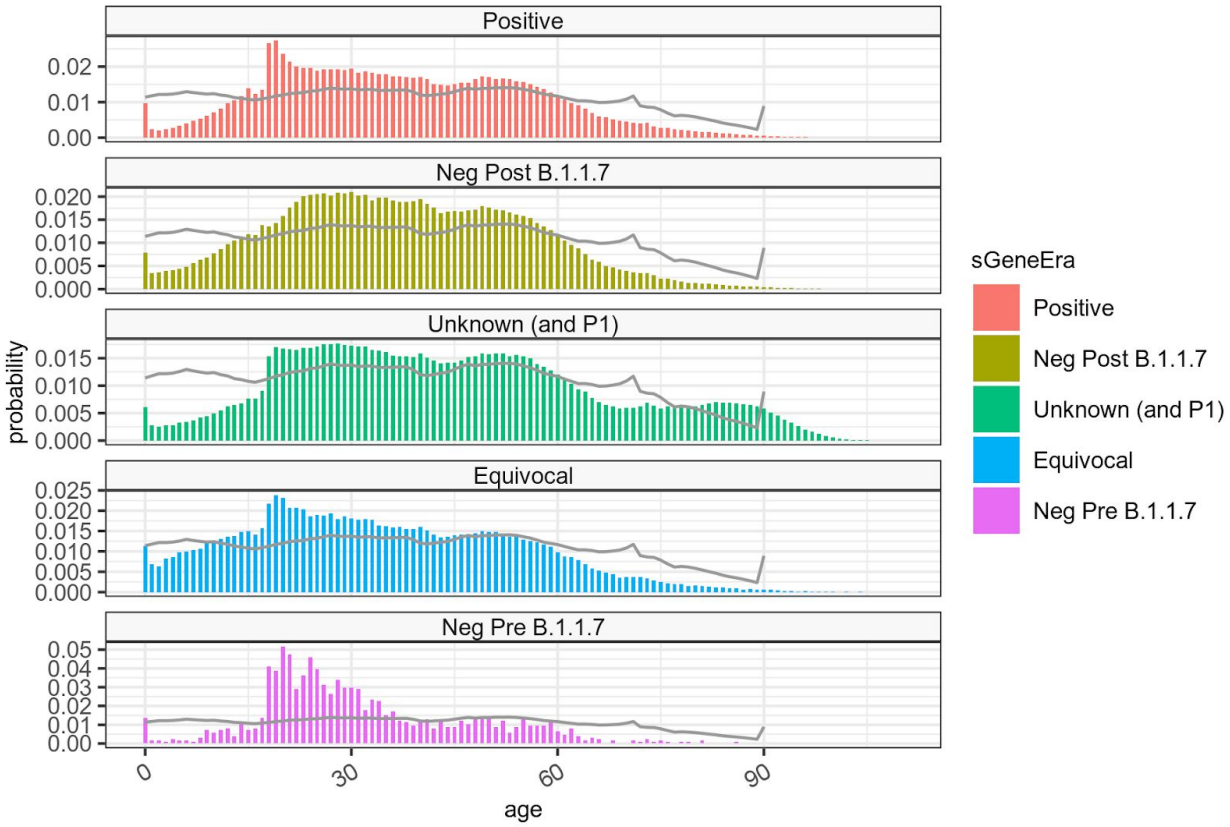
Pillar 2 testing is largely self selected, or driven by contact tracing. There remains a potential bias if there were a higher proportion of undetected asymptomatic cases in S gene negative infections than in S gene positive infections. In this event, S negative cases may be at a more advanced stage of infection when detected, and have a higher apparent mortality. This could be consistent with the lower N gene CT values observed in S gene negative cases. Our analysis, or any retrospective study based on symptomatic cases, would not be able to detect this. Addressing this potential bias requires a study design capable of detecting asymptomatic infections in S gene positives and S gene negatives.

There is no information about comorbid conditions in the data we analysed, although this will be partly controlled by age, ethnicity and index of multiple deprivation. It is possible that people with certain comorbidities are both more susceptible to infection with VOC-202012/1 and have a higher mortality, which could explain the increase in deaths observed.

Supplementary materials

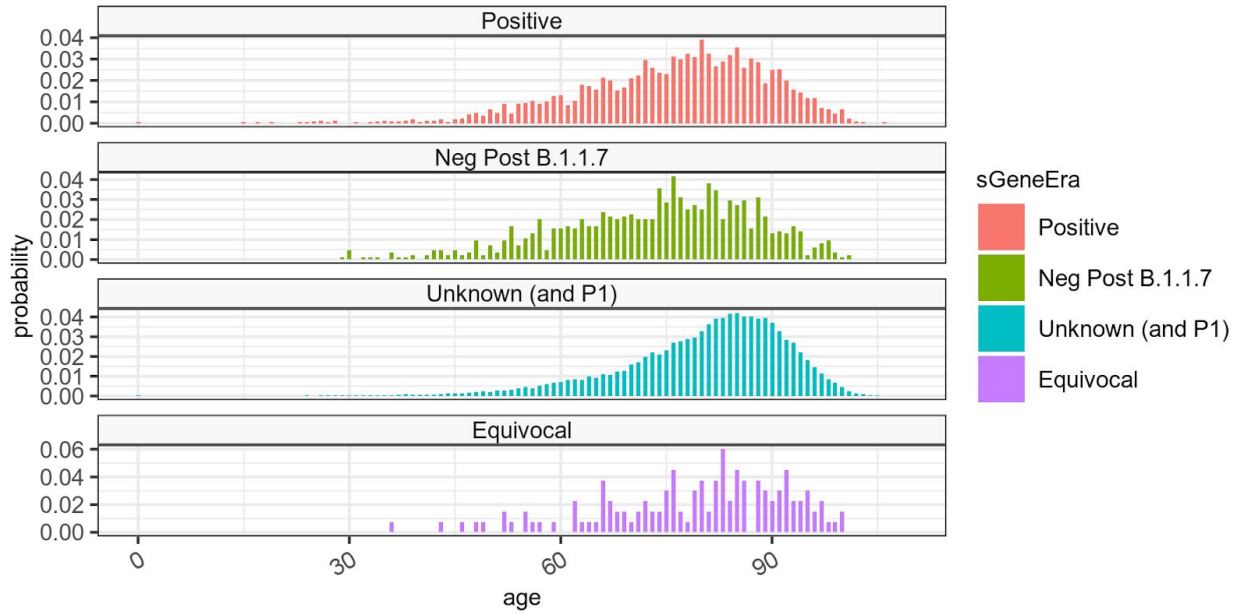
Age distributions of cases by sGene status

- Compared to pillar 1, pillar 2 cases are younger.
- Cases high in university age groups, compared to population levels (grey line).
- Older-old are under represented in Pillar 2.



Age distributions of infections by sGene status who died

- Deaths which had Pillar 2 tests slightly younger on average but no clear difference between pillar 2 S-negatives and S-positives.
- No deaths in S-negatives prior to 1st Oct 2020.

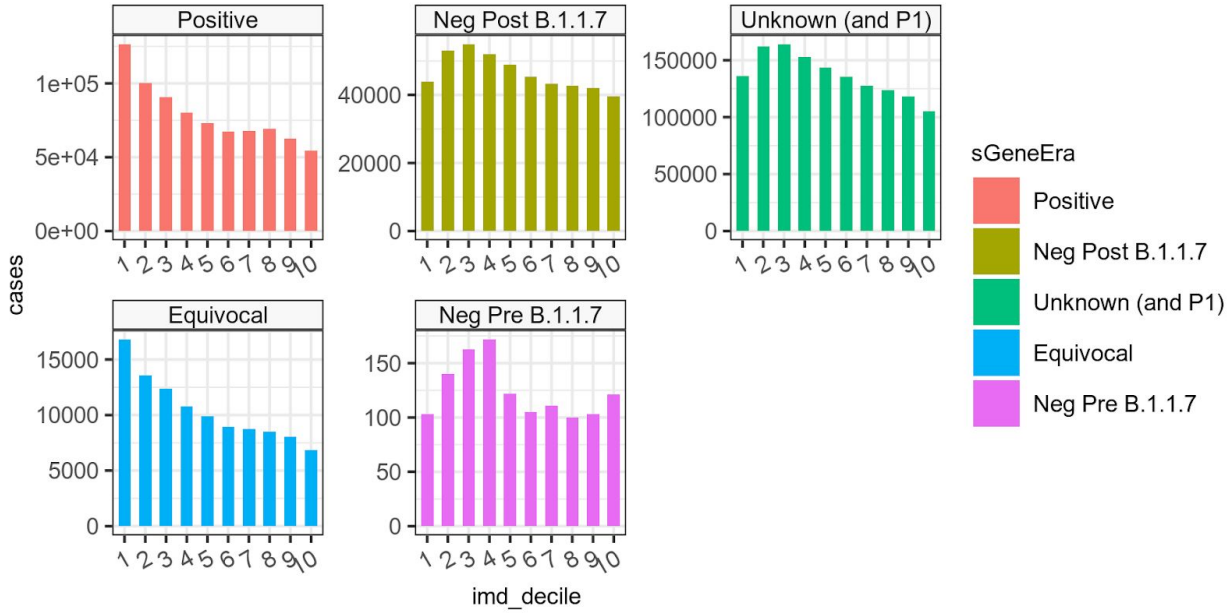


Summary statistics of full unmatched dataset

category	value	All N	All %age	All mean (SD)	Tested N	Tested %age	Tested mean (SD)	Died N	Died %age	Died mean (SD)	Died + Tested N	Died + Tested %age	Died + Tested mean (SD)
Age		2733654		41.0 (±20.9)	1364201		37.2 (±18.3)	52371		80.0 (±12.0)	3180		75.4 (±13.7)
Age by category	<30	922259	33.7%		519701	38.1%		124	0.2%		16	0.5%	
	30-59	1311931	48.0%		681883	50.0%		3306	6.3%		405	12.7%	
	60-69	220127	8.1%		103547	7.6%		5339	10.2%		522	16.4%	
	70-79	125981	4.6%		41184	3.0%		12311	23.5%		851	26.8%	
	80+	153356	5.6%		17886	1.3%		31291	59.7%		1386	43.6%	
Ethnicity	Afro-carribbean	120916	4.4%		50395	3.7%		1657	3.2%		67	2.1%	
	Asian	371999	13.6%		197406	14.5%		3691	7.0%		415	13.1%	
	Other	154523	5.7%		72902	5.3%		1271	2.4%		63	2.0%	
	White	2086216	76.3%		1043498	76.5%		45752	87.4%		2635	82.9%	
Gender	Female	1477342	54.0%		715544	52.5%		23532	44.9%		1345	42.3%	
	Male	1256312	46.0%		648657	47.5%		28839	55.1%		1835	57.7%	
IMD	1	275772	10.1%		131939	9.7%		5061	9.7%		279	8.8%	
	2	323430	11.8%		187403	13.7%		6684	12.8%		556	17.5%	
	3	329401	12.0%		167149	12.3%		6407	12.2%		420	13.2%	
	4	322465	11.8%		158311	11.6%		6084	11.6%		354	11.1%	
	5	296027	10.8%		143369	10.5%		5440	10.4%		306	9.6%	
	6	257609	9.4%		121926	8.9%		4956	9.5%		285	9.0%	
	7	247618	9.1%		120026	8.8%		4811	9.2%		247	7.8%	
	8	244322	8.9%		120371	8.8%		4700	9.0%		274	8.6%	
	9	231049	8.5%		112806	8.3%		4525	8.6%		254	8.0%	
	10	205961	7.5%		100901	7.4%		3703	7.1%		205	6.4%	
N gene CT		1364201		21.3 (±5.4)	1364201		21.3 (±5.4)	3180		19.8 (±5.2)	3180		19.8 (±5.2)
Region	East of England	288326	10.5%		100325	7.4%		5948	11.4%		195	6.1%	
	London	526755	19.3%		217627	16.0%		7285	13.9%		282	8.9%	
	Midlands	513069	18.8%		260618	19.1%		11076	21.1%		645	20.3%	
	North East and Yorkshire	443023	16.2%		294506	21.6%		9555	18.2%		909	28.6%	
	North West	435031	15.9%		292682	21.5%		8340	15.9%		711	22.4%	
	South East	374066	13.7%		156386	11.5%		7227	13.8%		314	9.9%	
	South West	153384	5.6%		42057	3.1%		2940	5.6%		124	3.9%	
S gene	Positive	792327	29.0%		792327	58.1%		2206	4.2%		2206	69.4%	
	Neg Post B.1.1.7	466057	17.0%		466057	34.2%		841	1.6%		841	26.4%	
	Unknown (and P1)	1369453	50.1%					49191	93.9%				
	Equivocal	104577	3.8%		104577	7.7%		133	0.3%		133	4.2%	
	Neg Pre B.1.1.7	1240	0.0%		1240	0.1%							
Status	Dead <28 days	52371	1.9%		3180	0.2%		52371	100.0%		3180	100.0%	
	Other	2681283	98.1%		1361021	99.8%							

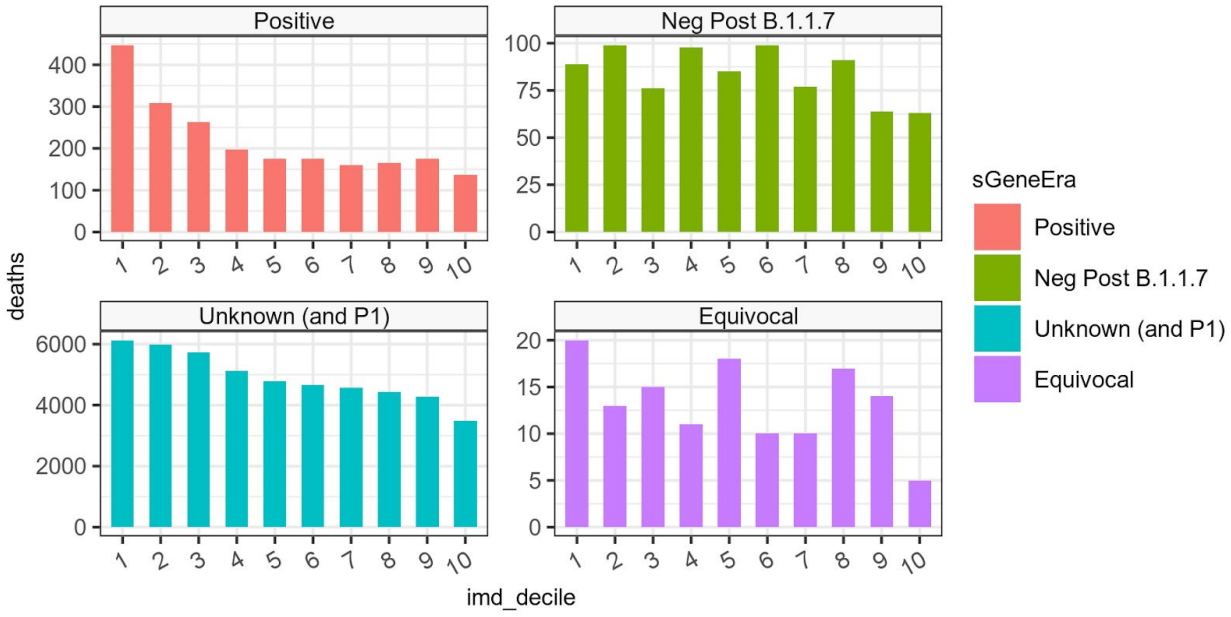
Cases by Index of Multiple Deprivation

- Difficult to explain patterns in relative incidence by IMD, which varies by pillar.
- Not uniform across the different pillars and between S Gene status.



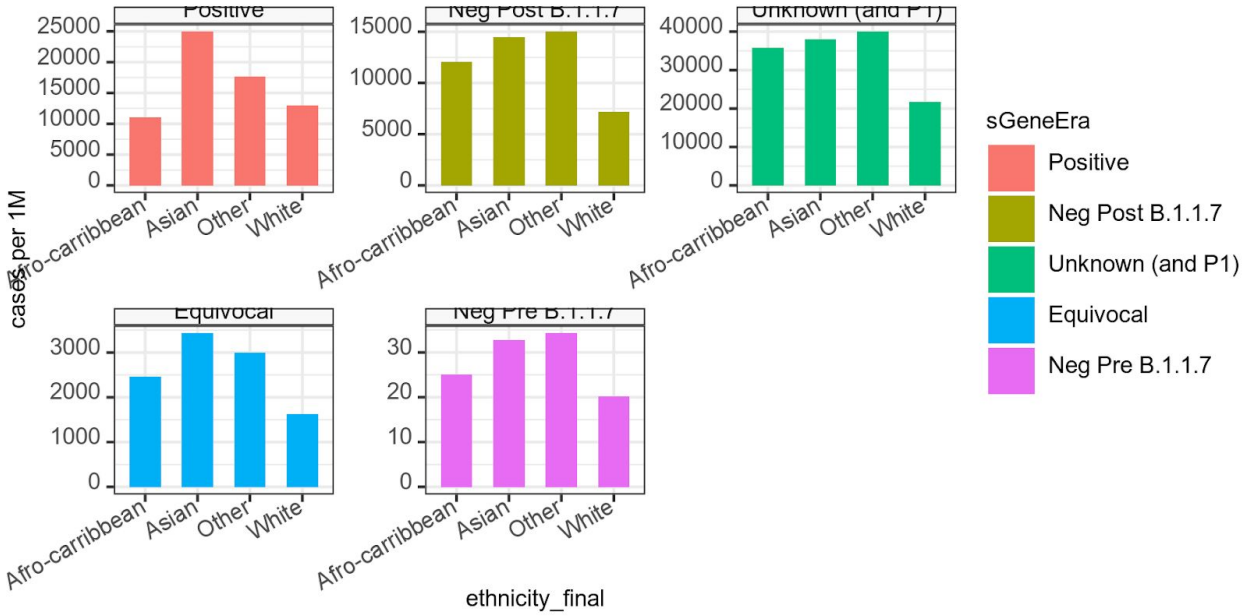
Deaths by Index of Multiple Deprivation

- Deaths higher in lower IMD groups. This is not terribly consistent with cases across the various data sources.



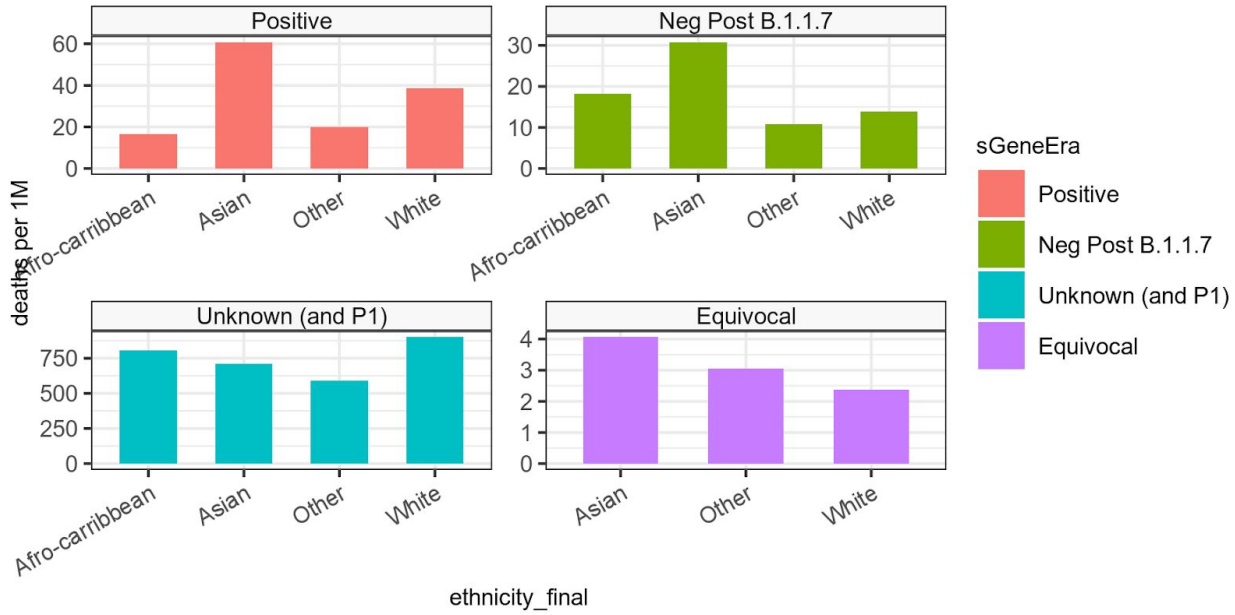
Cases per 1M by Ethnicity

- Potentially sampling not uniform across ethnic groups. May represent test and trace activity.



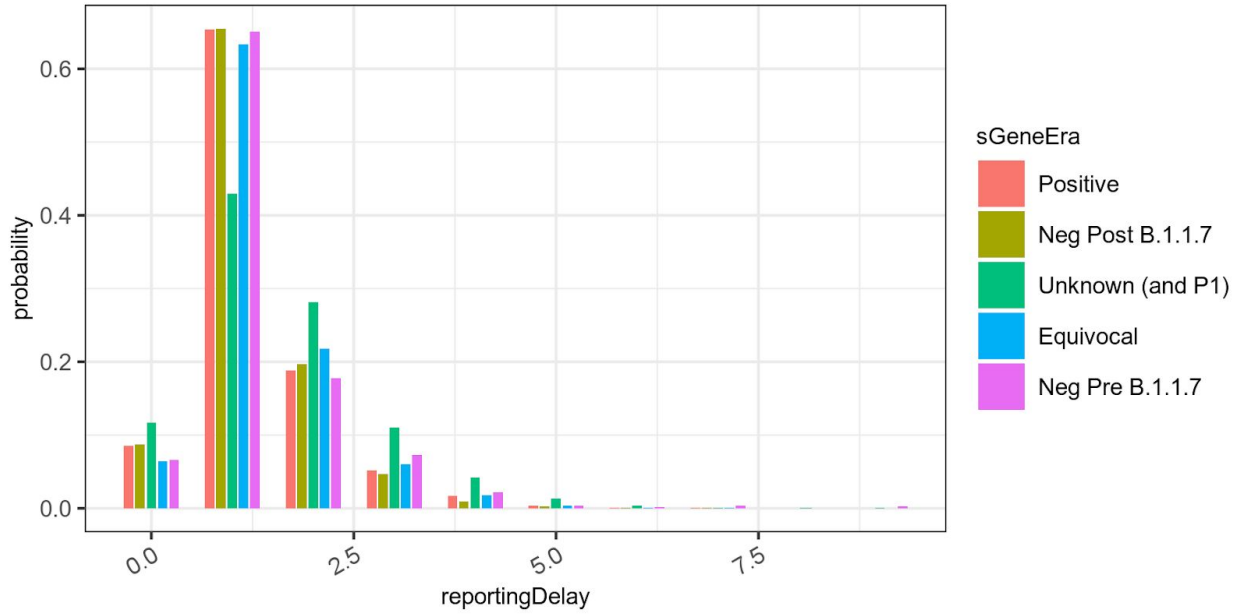
Deaths per 1M by Ethnicity

- Deaths are over-represented in Asian communities in Pillar 2 versus Pillar 1 positive cases



Test reporting delay versus S Gene status

- Pillar 1 tests have in the past taken longer to be processed than pillar 2.
- We would expect testing turnaround times to be dynamic and depend on demand.



Time to admission versus S Gene status in those that have died

- From the time of positive specimen sample there are differences in the time to admission depending on the source of data.
- This delay is only known for patients who go on to die.