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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Frampton D, Rampling T, Cross A, et al. Genomic characteristics and clinical effect of the emergent SARS-CoV-2 B.1.1.7 lineage in London, UK: a whole-genome sequencing and hospital-based cohort study. *Lancet Infect Dis* 2021; published online April 12. https://doi.org/10.1016/S1473-3099(21)00170-5.

Supplementary methods:

Comorbidities: Comorbidities were graded according to the presence of 0,1 or ≥2 of the following:

Chronic cardiac disease; chronic respiratory disease (excluding asthma); chronic renal disease (estimated glomerular filtration rate ≤30); mild-to-severe liver disease; dementia; chronic neurological conditions; connective tissue disease; diabetes mellitus (diet, tablet or insulin-controlled); HIV/AIDS; malignancy; clinician-defined obesity.

This list is based on a modified Charlson index and is the same as defined in the ISARIC 4C COVID-19 Mortality Score (https://isaric4c.net/risk/4c/)

Definitions:

Pillar 1 tests: these are SARS-CoV-2 tests (usually PCR) carried out in Public Health England laboratories and National Health Service (NHS) laboratories for patients and staff who work in health and social care.

Pillar 2 tests are SARS-CoV-2 diagnostic tests (PCR or other rapid diagnostic tests including lateral flow assays) carried out for and in the community.

Vaccination status:

The first person in the UK was vaccinated on 8th December 2020 and in the initial weeks of vaccine roll-out, eligibility was tightly controlled by age (over 80yrs old) and care home residents and staff.

According to NHS data, 521,594 individuals in England had received a COVID vaccination by 20th December (https://www.england.nhs.uk/statistics/wp-content/uploads/sites/2/2020/12/COVID-19-total-announced-vaccinations-24-December-2020-1.pdf). Although this figure would have included health care staff (including several authors on this paper), if we assume all 521,594 doses were given to the 3.2 million >80 yr olds in England, we can extrapolate that approximately 16% of over 80yr olds were vaccinated by 20th December.

In our cohort, we included only 24 individuals who had a positive test and sequence data and were admitted on or after 8th December. It is possible, therefore, that approximately 4 patients in our analysis had received a COVID vaccine prior to admission, albeit with insufficient time to mount an immune response affecting the presence of variant vs non-variant SARS-CoV-2. Further, there were very few vaccination centres active during the period 8-20th December; our local vaccination centre did not start vaccinating until 21st December. We therefore conclude that the COVID-19 vaccination has a negligible effect on our study

Supplementary Tables and Figures

Patient State	Descriptor	Score
Uninfected	Uninfected; no viral RNA detected	0
Ambulatory mild disease	Asymptomatic; viral RNA detected	1
	Symptomatic; independent	2
	Symptomatic; assistance needed	3
Hospitalised: moderate disease	Hospitalised; no oxygen therapy	4
	Hospitalised; oxygen by mask or nasal prongs	5
Hospitalised: severe disease	Hospitalised; oxygen by NIV or high flow	6
	Intubation and mechanical ventilation, pO2/FiO2 ≥150 or SpO2/FiO2 ≥200	7
	Mechanical ventilation pO2/FIO2 <150 (SpO2/FiO2 <200) or vasopressors	8
	Mechanical ventilation pO2/FiO2 <150 and vasopressors, dialysis, or ECMO	9
Death	Dead	10

Supplementary Table 1: WHO Ordinal Scale for the Assessment of COVID-19 Disease Severity. Reproduced from Lancet Infect Dis 2020; 20: e192–97. This table gives a common outcome measure set for COVID-19 as described by the WHO Working Group on the Clinical Characterisation and Management of COVID-19 infection. For the purposes of this study, severity of illness of patients admitted to hospital were derived by recording the highest point reached on this ordinal scale by day 14 after symptom onset, or from first positive swab date if asymptomatic. Patients with severe disease were defined as those patients reaching point 6 or higher during the assessment period. Mortality data as defined by death by day 28 after first positive swab was also collected. RNA = Ribonucleic acid; NIV = non-invasive ventilation; pO2 = arterial partial pressure of oxygen; FiO2 = fractional inspired oxygen; SpO2 = peripheral capillary oxygen saturation; ECMO = extracorporeal membrane oxygenation.

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Supplementary Table 2. Acknowledgement for GISAID SARS-CoV-2 sequences used as references for phylogenetic analysis.

We gratefully acknowledge the following Authors from the Originating laboratories responsible for obtaining the specimens and the Submitting laboratories where genetic sequence data were generated and shared via the GISAID Initiative, on which this research is based. All submitters of data may be contacted directly via www.gisaid.org

Shu, Y., McCauley, J. GISAID: from vision to reality *Euro Surveill*, 2017;**22**(13) doi:10.2807/1560-7917.ES.2017.22.13.30494

Supplementary Table 3: Cohort characteristics by outcome WHO level ≥6 and/or death (n=339)

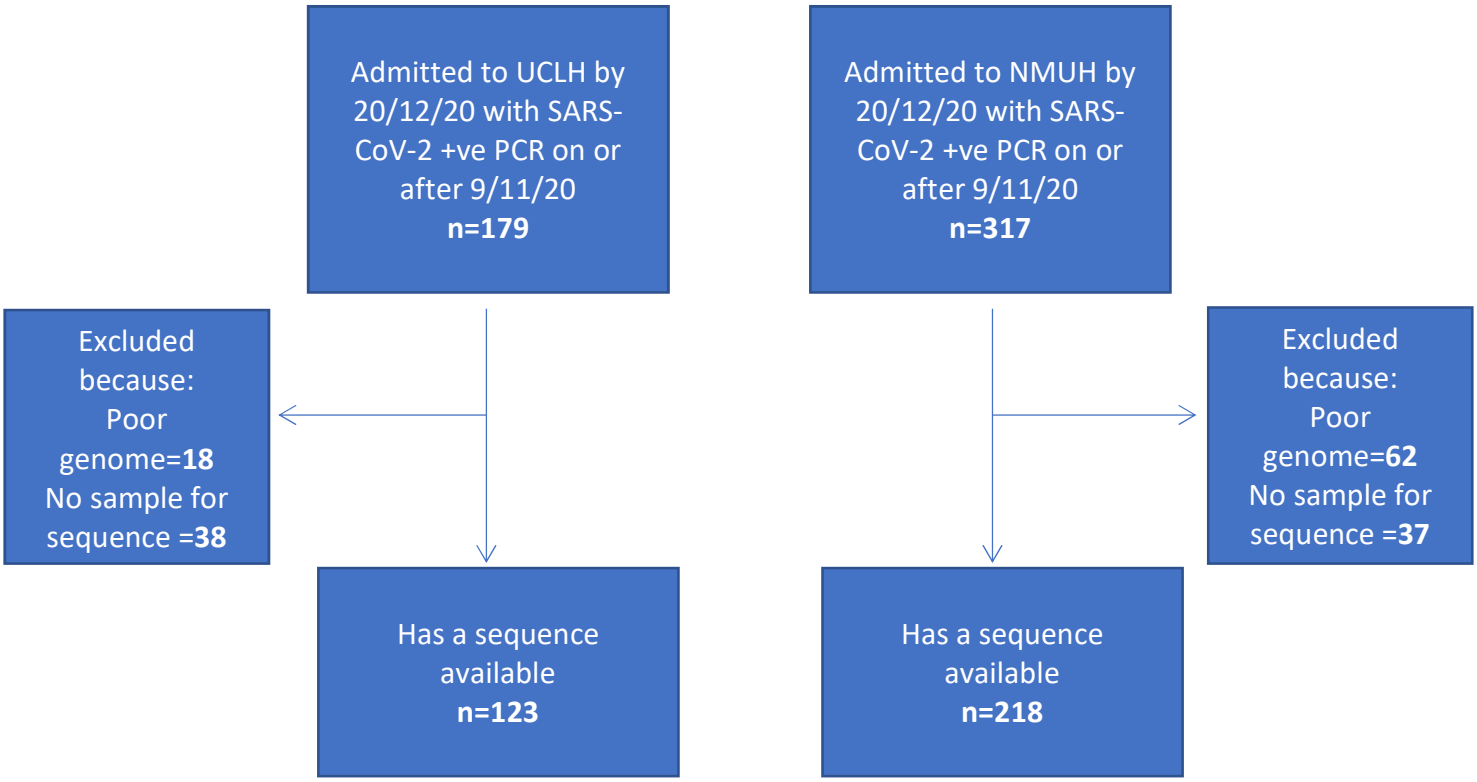
	WHO level <6		Severe disease: WHO level ≥6 and/or death		*p* value for chi-squared test* or Fisher's exact test
	n	%	n	%	
Variant (n=339)					
Non-B.1.1.7	88	41	53	42	0.818
B.1.1.7	126	59	72	58	
Hospital (n=339)					
NMUH	125	58	91	73	0.008
UCLH	89	42	34	27	
Sex (n=339)					
Female	122	57	58	46	0.059
Male	92	43	67	54	
Age (years) (n=339)					
≤45	63	29	15	12	<0.001
46-59	58	27	30	24	
60-74	49	23	39	31	
≥75	44	21	41	33	
Ethnicity (n=292)					
White	106	59	65	59	0.999
Ethnic minority	75	41	46	41	
BMI (n=194)					
<25	46	40	29	37	0.921
25-29.9	27	23	23	29	
≥30	43	37	26	33	
Hospital acquired SARS-CoV-2 infection (n=339)					
Community	193	90	118	94	0.221
Hospital (possible, probable, definite)	21	10	7	6	
Comorbidity score (n=336)					
0	79	37	27	22	<0.001
1	56	26	29	23	
≥2	77	36	68	55	

*** For ordinal variables, chi-squared test for trend was used**

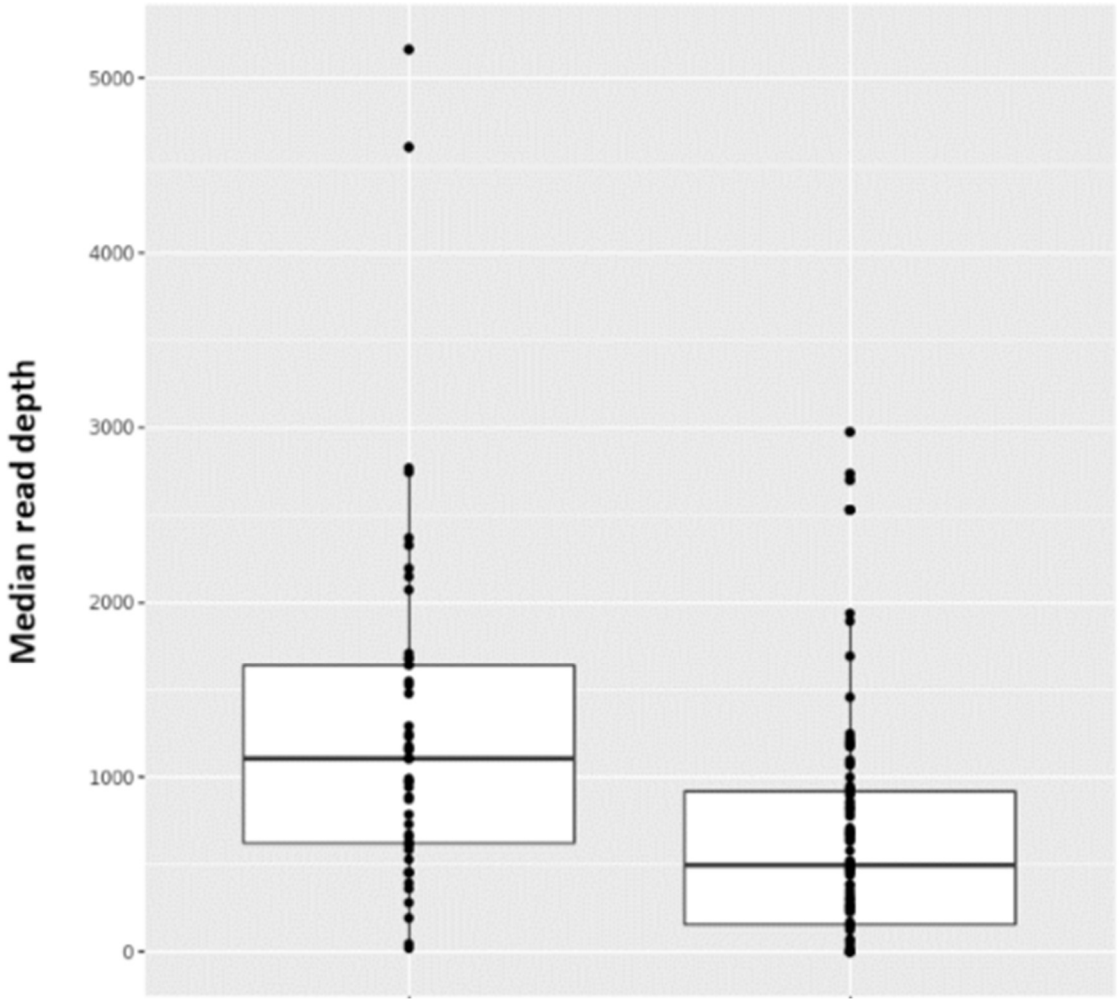
Supplementary Table 4: WHO categorisation of disease severity by variant

Categories used in main analysis	WHO categorisation†	Non-B.1.1.7 (n=141)	B.1.1.7 (n=198)
"non-severe"	Ambulatory mild disease or hospitalised but no oxygen therapy	46 (33%)	38 (19%)
	Hospitalised: oxygen, by mask/nasal prongs	42 (30%)	88 (44%)
Severe disease and/or death (outcome)	Non-invasive ventilation/ high flow oxygen	26 (18%)	29 (15%)
	Intubation and mechanical ventilation with/without additional organ support	3 (2%)	12 (6%)
	Death	24 (17%)	31 (16%)

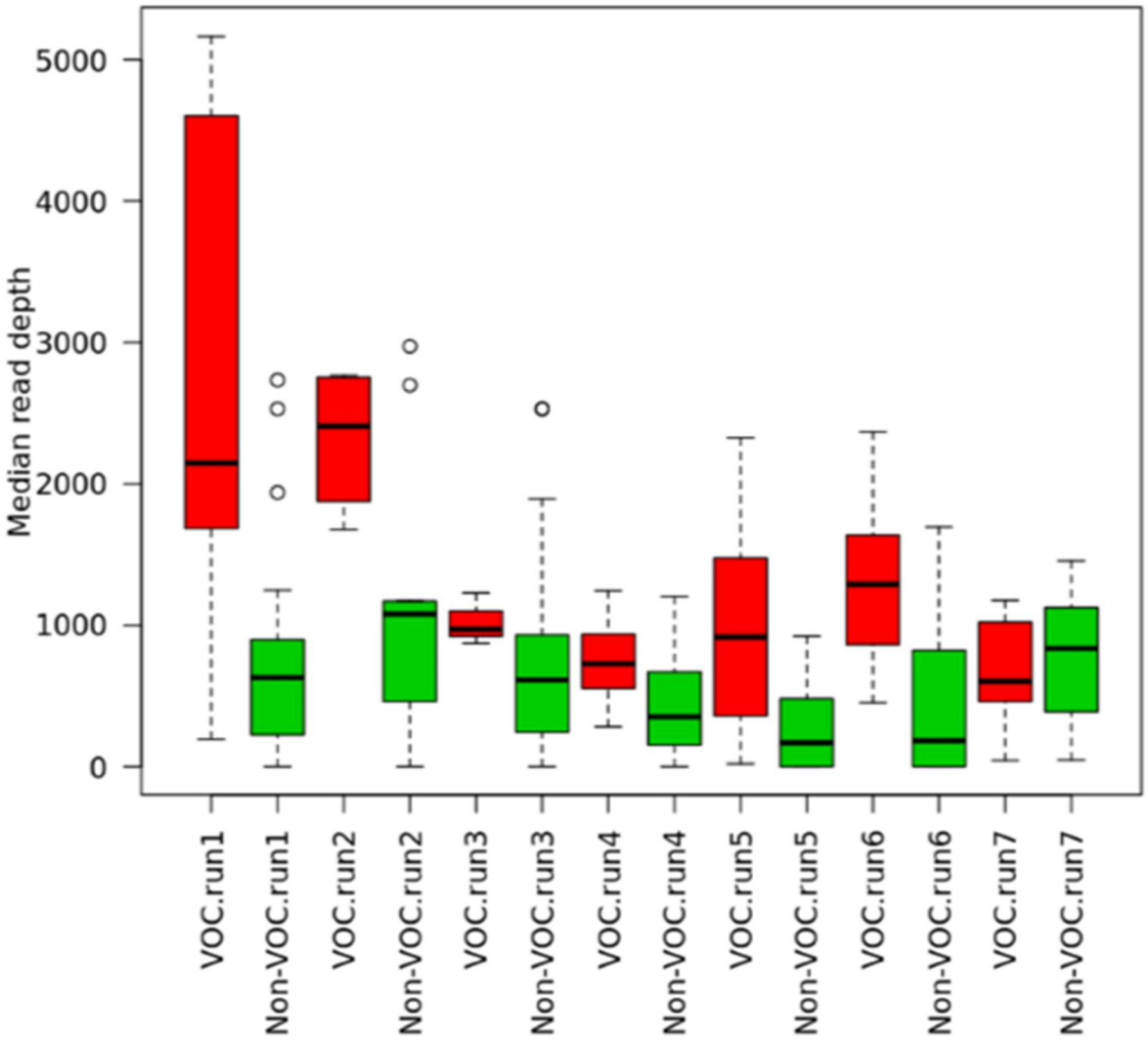
†Death reported by day 28 after first positive SARS-CoV-2 PCR test; all other categories are the highest level of care received within 14 days of symptom onset or positive test.



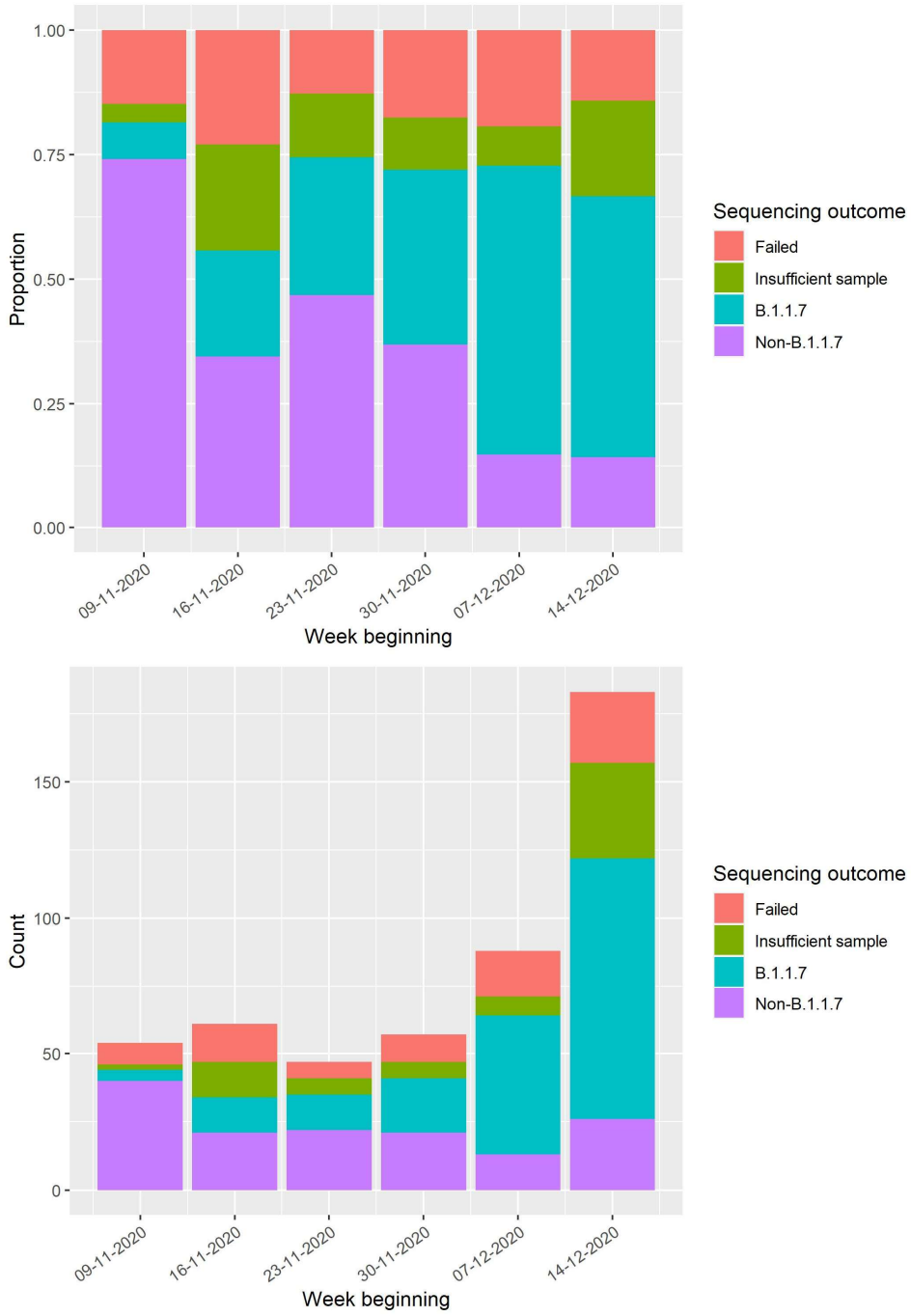
Supplementary Figure 1. Overview of UCLH and NMUH study cohorts.



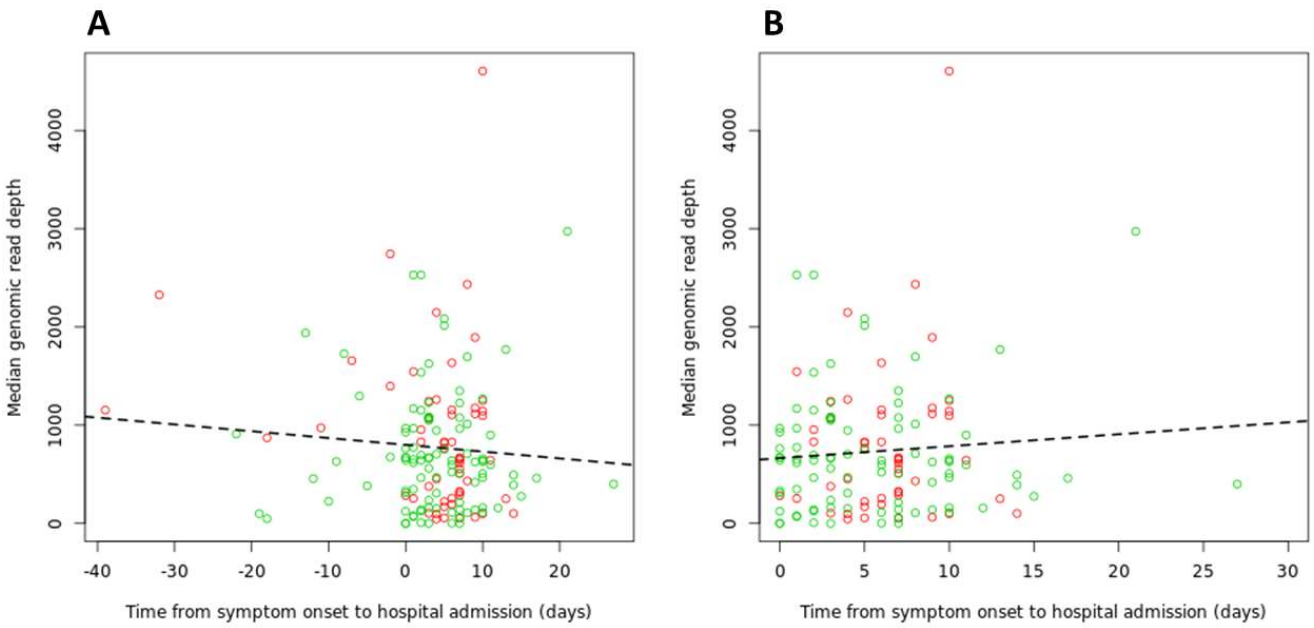
Supplementary Figure 2: **Boxplots showing the increased genomic median read depths observed across all samples for B.1.1.7 compared to non-B.1.1.7 genomes.** Read depths at each genomic position were obtained for each sample from mpileup files; where sequencing had failed (e.g. due to amplicon failure) we assigned positional read depths of 0. Median read depths at each position could then be calculated for B.1.1.7 and non-B.1.1.7 samples by taking the median read depth at each position across each sample set, after mapping genomic coordinates for each sample to a common reference (Wuhan-Hu-1, NC_045512.2).



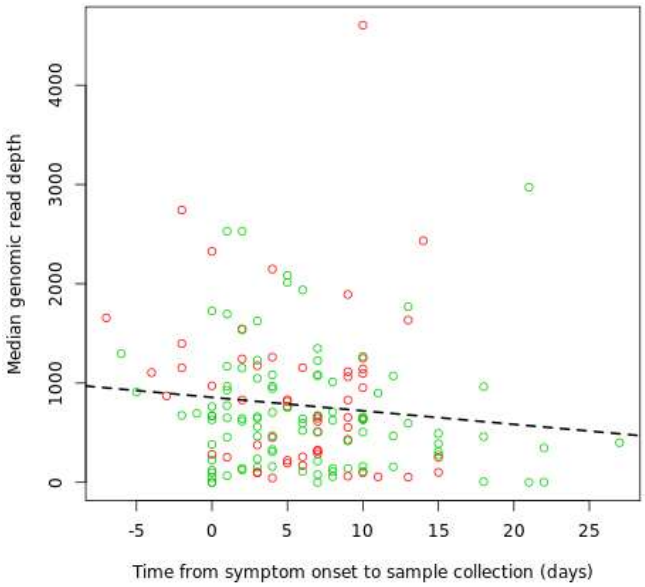
Supplementary Figure 3. Boxplots showing variation in genomic median read depth, grouping B.1.1.7 and non-B.1.1.7 samples by sequencing run. Whilst there is clear variation between runs due to experimental batch effects, in 6/7 runs B.1.1.7 samples have greater median read depths across their genomes. Read depths at each genomic position were obtained for each sample from mpileup files; where sequencing had failed (e.g. due to amplicon failure) we assigned positional read depths of 0. Median read depths at each position could then be calculated for B.1.1.7 and non-B.1.1.7 samples by taking the median read depth at each position across each sample set, after mapping genomic coordinates for each sample to a common reference (Wuhan-Hu-1, NC_045512.2).



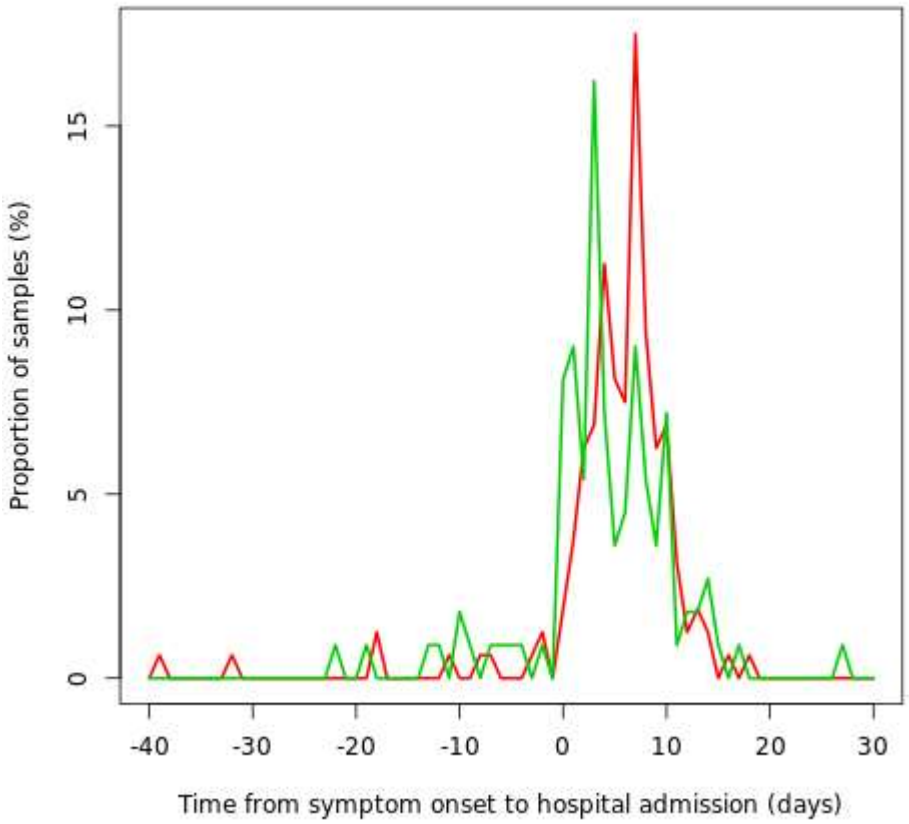
Supplementary Figure 4. Stacked proportional and absolute count bar charts showing sequencing outcome in eligible patients by week over the study period. Failed indicates patients whose samples were sequenced but failed to generate an adequate genome on analysis. Insufficient sample indicates patients that did not have sufficient sample for sequencing. An additional 7 positive SARS-CoV-2 PCR samples were obtained from this patient cohort in the week beginning 21st December 2020 not included in the above charts. Of these 1 was successfully sequenced and 6 had insufficient sample. Chi-squared test for trend for failed sequence vs other; p=0.745.



Supplementary Figure 5. Comparing median genomic read depth with time from symptom onset to hospital admission. B.1.1.7 samples are shown in red, non-B.1.1.7 lineages in green. Distributions are shown for: (a) all patients; (b) patients presenting as symptomatic on arrival at the hospital only. Linear regression trend lines are shown for reference: (a) r^2=0.0064; (b) r^2=0.0062. We found no correlation between read depth and time from symptom onset to hospital admission for these samples: (a) r_s=-0.08, p=0.32; (b) r_s=0.0066, p=0.94. Read depths at each genomic position were obtained for each sample from mpileup files; where sequencing had failed (e.g. due to amplicon failure) we assigned positional read depths of 0. Median read depths at each position could then be calculated for B.1.1.7 and non-B.1.1.7 samples by taking the median read depth at each position across each sample set, after mapping genomic coordinates for each sample to a common reference (Wuhan-Hu-1, NC_045512.2).



Supplementary Figure 6. Comparing median genomic read depth with time from symptom onset to date of sample collection. B.1.1.7 samples are shown in red, non-B.1.1.7 lineages in green. Distributions are shown for all patients. A linear regression trend line is shown for reference (r^2=0.013). We found a weak correlation between read depth and time from symptom onset to date of sample collection for these samples (r_s=-0.17, p=0.032), suggesting a general decline in viral load over the course of infection. Read depths at each genomic position were obtained for each sample from mpileup files; where sequencing had failed (e.g. due to amplicon failure) we assigned positional read depths of 0. Median read depths at each position could then be calculated for B.1.1.7 and non-B.1.1.7 samples by taking the median read depth at each position across each sample set, after mapping genomic coordinates for each sample to a common reference (Wuhan-Hu-1, NC_045512.2).



Supplementary Figure 7. The distribution of time from symptom onset to hospital admission for cohort study samples. The distribution for B.1.1.7 patients is shown in red, non-B.1.1.7 patients are shown in green. Median time from symptom onset to hospital admission for B.1.1.7 is higher for B.1.1.7 patients than non-B.1.1.7 patients: 6(4-8) days vs. 4(1-8) days. However, this difference is not significant: mean time: 5.1(6.6) vs. 3.9(6.8) days, p=0.15.

Supplementary Table 5: Patient demographics for the long-shedding and remdesivir treated cohorts

	Long shedding cohort (n=34)	Remdesivir cohort (n=32)
Sex		
Male	23	20
Female	11	12
Ethnicity		
White	21	20
Non-white	10	11
Unknown	3	1
Age		
Range	14-84	34-81
Median	62	60
IQR	48-73	46-72