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SARS-CoV-2 viral dynamics in infections with variants of concern in the French community

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Abstract

We analysed 871,604 PCR tests performed in the community in the Paris area (France) from 1st January 2021 to 24th March 2021. The PCR cycle threshold (Ct) at symptom onset was -1.33 (95% CI $[-1.59, -1.07]$) and -1.15 (95% CI $[-1.57, -0.697]$) lower for individuals infected with B.1.1.7 and B.1.351 compared to other strains. The mean duration of infectiousness after symptom onset (time to Ct > 31) was 8.6, 9.3, 8.9 days for individuals infected with historical strains, variants B.1.1.7 and B.1.351. This study clarifies the post-symptom intra-host dynamics of B.1.1.7 and B.1.351 and suggests that higher peak viral load for these variants may explain part of their evolutionary advantage and the greater pathogenicity of B.1.1.7.

Introduction

Several genetic variants of SARS-CoV-2 with potentially concerning phenotypic consequences were identified at the end of 2020. The B.1.1.7 variant of SARS-CoV-2 (also called VOC-202012/01 or 501Y.V1), first detected in England in September 2020, rapidly rose in frequency in October 2020 in the United Kingdom and spread in multiple countries (1–5). Viruses of this lineage are 50% to 100% more transmissible, have a 60% higher infection fatality ratio (6–8), confer a higher viral load (9–12) and may cause longer infection (10,13). Less is known of the variant B.1.351 / 501Y.V2, which was first detected in South Africa, and also appears more transmissible or able to escape existing immunity and to confer a higher viral load (12,14). Studying intra-host dynamics in a large number of individuals is important (i) to understand pathogenesis and the link between viral load dynamics and disease severity, (ii) to determine if variants of concern are associated to higher viral loads that could lead to greater transmissibility, and (iii) to adapt if necessary the duration of isolation of infected individuals. We used data from 871,604 PCR tests conducted by a large private clinical laboratory in the community in the Ile-de-France region of France from 1st January to 24th March 2021 (17% of all tests in this period). We compared the within-host dynamics of viral load in symptomatic individuals infected by suspected variants of concern B.1.1.7 and B.1.351 to other strains.

Methods

Starting from all tests, negative and positive ($N = 871,604$), we retained 16,134 tests conducted on 12,858 symptomatic individuals for the main analysis. These include all individuals with at least one positive test and associated data on Ct value, sex, age, variant and PCR method (Table 1, Supplementary Figure 1).

We conducted all analyses on the Ct value combining the two Ct values obtained with two primers targeting the RNA-dependent RNA polymerase (RdRp) gene, the most sensitive assays. Both Ct values were highly correlated with a regression coefficient close to 1. All Ct values above 36 were set to undetectable. Individuals are considered infectious below $Ct = 31$. When two Ct values were present at the same time point and detectable, we used the mean of the two values. When only one of the two Ct values was present or detectable, we used it and ignored the other. If both Ct values were undetectable, we set the Ct to undetectable.

Variants were detected using two PCRs targeted at the spike deletion 69-70 and at the spike substitution N501Y (IDTM SARS-CoV-2/UK/SA Variant Triplex). Combination of del69-70 and substitution N501Y was interpreted as suspicion of the B.1.1.7 variant. Substitution N501Y

without del69-70 was interpreted as suspicion of the B.1.351 variant. The variant P.1/501Y.V3 was nearly absent in France in the period considered. It was detected in only 10/3429, 9/5472, 41/6592 sequences collected in January, February, March in France according to the GISAID database.

We relied on self-reporting of symptom onset dates. At each test, individuals were asked to declare whether they had symptoms, and what was the date of symptom onset (if any): [0, 3] days ago, [4, 7] days ago, [8, 14] days ago or 15 or more days ago. For individuals with repeated tests, we retained only those for which the timing of symptoms declared at the different visits were consistent with an error margin of two days. For each individual with consistent declarations, we set the time of symptoms to the mean of the earliest possible date and the latest possible date of symptoms.

The censored mixed-effects linear regression describing Ct value as a function of time since symptoms and other covariates was conducted within the R package lme4, developed to analyse viral load data truncated at the detection limit of the assay (15). The method treats the viral loads as right-censored (at Ct=36) and infers the maximum likelihood parameters with an expectation-maximization algorithm. We used a normal random effect to represent inter-individual variability in the intercept (Ct at symptom onset). To select a model, we started from the full linear model predicting viral load as a function of time since symptom onset (continuous variable), variant (historical strains, suspected B.1.1.7, suspected B.1.351), age category (10 categories, 0-9, 10-19, ..., 80-89, 90+ years old), and the three pairwise interactions. We assessed the significance levels of each of the interactions, comparing with likelihood ratio test (LRT) the model without the focal interaction to the full model. We also tested the significance of each of the three main effects by comparing with LRT the model without the focal main effect to the model with the three main effects. Confidence intervals were computed using the multivariate normal distribution of the errors on the fixed effects.

Results

Among the 12,858 individuals, most had one test (N = 10,225), 2,121 individuals had two tests and the rest (N = 512 individuals) had three or more tests (Table 1). From the linear regression, there was no significant interaction for viral load between variant and age ($p = 0.31$) and we therefore present results of the simplified model without this interaction.

The predicted viral load at symptom onset was inferred to be 22.7 Ct on average (95% confidence interval, CI, [22.4 – 23.0]) for historical strains (Supplementary Table 1). The inter-

individual standard deviation in viral load at symptom onset was 2.9, meaning that 95% of symptomatic individuals had a viral load at symptom onset between 28.4 and 17.0. The viral load declined on average at a rate of +0.97 Ct per day [0.93 - 1.0]. The viral load at symptom onset was higher in B.1.1.7 and B.1.351 variants than in historical variants, with a Ct value -1.33 [-1.59, -1.07] and -1.15 [-1.57, -0.697] lower than historical strains for B.1.1.7 and B.1.351 respectively ($p < 10^{-16}$). The viral load of the two variants declined slightly faster than that of the historical strains with an additional decline rate of +0.06 [0.015; 0.10] and +0.095 [0.018; 0.16] per day for B.1.1.7 and B.1.351 respectively ($p = 0.0004$). The duration of shedding was longer for individuals infected by variants: the mean time to a Ct of 31, the limit above which the individual is no longer infectious, was 8.6, 9.3 and 8.9 days for historical strains, B.1.1.7 and B.1.351 (Figure 1B). The mean time to a Ct of 36, the limit above which the virus is fully cleared, was 13.7, 14.2 and 13.6 days for historical strains, B.1.1.7 and B.1.351. There is substantial inter-individual variability around these mean values (Figure 1C). We based most of our analyses on the Ct value of the PCR targeting the RdRp gene, but results were very consistent when analyzing the Ct value of the nucleocapsid gene (N), with an even stronger effect of the variants on viral load at symptom onset (effect sizes -1.81 [-2.32; -1.32] and -2.11 [-2.38; -1.81] for B.1.1.7 and B1.351) (Supplementary Table 2, Supplementary Figure 2).

Discussion

Both B.1.1.7 and B.1.351 variants conferred a higher viral load at symptom onset. The main strengths of our study are the control for time since symptoms, which improves the comparison between historical strains and variants, and the large number of tests, in particular for both B.1.1.7 and B.1.351 variants.

However, several limitations must be noted. We used data from community testing in Ile-de-France. This ensures a large number of tests, but tests are not done systematically and in a random sample of individuals. The date of symptom onset was self-reported. We excluded individuals with inconsistent symptoms dates, but consistency was impossible to assess for the vast majority of individuals with a single test. To address some of these limitations, we ran the same analysis on the more complete dataset where the time from symptom onset was not necessarily known (41,489 tests representing 33,391 individuals), and considered the time since first positive test instead of the self-reported time since symptom onset. Results were very consistent with those of the main analysis (Supplementary Table 3). In addition, individuals declaring symptoms at all their tests had a larger viral load than asymptomatic individuals

(-0.95 , CI [-1.1 , -0.83]). A last limitation is that variant assignation is based on PCR screening. The suspected B.1.1.7 and B.1.351 were not confirmed by whole genome sequencing. In Ile-de-France, whole-genome sequencing of a random subset of 609 cases on March 2nd 2021 quantified the prevalence of B.1.1.7 at 76% of interpretable sequences (16). Thus the vast majority of viruses with substitution N501Y and spike deletion 69-70 must be B.1.1.7, as observed in the United Kingdom when the prevalence of B.1.1.7 was substantial (1). The prevalence of B.1.351 in France was 6.5%, and the prevalence of P.1 (first detected in Japan in travelers from Brazil) was 0.3% (16). If only clades B.1.351 and P.1 carried N501Y without del69-70, then 96% of the suspected B.1.351 are true B.1.351.

The evidence presented here from thousands of PCR tests can be compared with densely sampled trajectories of seven individuals infected with B.1.1.7 (13). There, individuals infected with B.1.1.7 had a -1.2 Ct higher viral load than those infected with the historical strains, very similar to our estimate of -1.33 . The authors detected a longer time to clearance ($+1.8$ days) for individuals infected with B.1.1.7. In our case, clearance (time to threshold Ct 36) was also slightly longer for B.1.1.7 ($+0.49$ days) and exclusively the result of the higher peak viral load.

To conclude, using 16,134 tests representing 12,858 symptomatic individuals tested positive in the community in Ile-de-France region of France from 1st January 2021 to 24th March 2021, we found that infection by suspected B.1.1.7 and B.1.351 variants strongly impacted the viral load at symptom onset at all ages. Higher viral load could partly explain the greater pathogenicity of B.1.1.7. It could also explain the selective advantage of B.1.1.7 through a transmission advantage (17). Individuals infected by suspected B.1.1.7 and B.1.351 excreted virus (Ct < 31) for only slightly longer than those infected by historical strains. This does not preclude the possibility that the mean generation time is longer for individuals infected by these strains, as we did not study the pre-symptomatic phase which could also play a role (13). Larger datasets with systematic PCR tests and capturing the pre-symptomatic phase will improve our understanding of infection by SARS-CoV-2 variants of concern and their potential epidemiological consequences.

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Competing interests

JG has worked as consultant for ROCHE Company.

Biographical sketch of first author

GC is a PhD student working on the exit mechanisms of respiratory syncytial virus in the INSERM U1173 team led by Marie-Anne Rameix-Welti. In parallel to her PhD thesis, she works as a researcher in the scientific committee of the Biogroup laboratory.

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Strain	N	Sex		Age category										Time from symptom onset (days)					Number of tests		
		Female	Male	0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	≥ 90	< 0	[0, 2[[2, 6[[6, 12[≥ 12	1	2	≥ 3
Historical	3272	54.3	45.7	1.65	9.32	19.5	21.2	20.2	15.8	7.21	3.51	1.41	0.183	3.18	55.9	13.4	14.3	13.2	52.7	30	17.4
B.1.351	1366	54.9	45.1	1.61	11.6	20	23.2	20.7	13.9	5.56	2.49	0.586	0.366	3.59	59.2	12.6	14.6	10.1	54.4	32.2	13.4
B.1.1.7	11496	55.3	44.7	1.85	11.4	19.6	21.5	20.6	14.6	6.6	3.01	0.6	0.27	1.87	66.8	12	11.6	7.79	67.5	24.5	7.97

Table 1: Overview of the test data: number of tests, and percentages of each sex, age category, time from symptom onset category, and number of tests per individual for historical strains and, B.1.351 and B.1.1.7 variants.

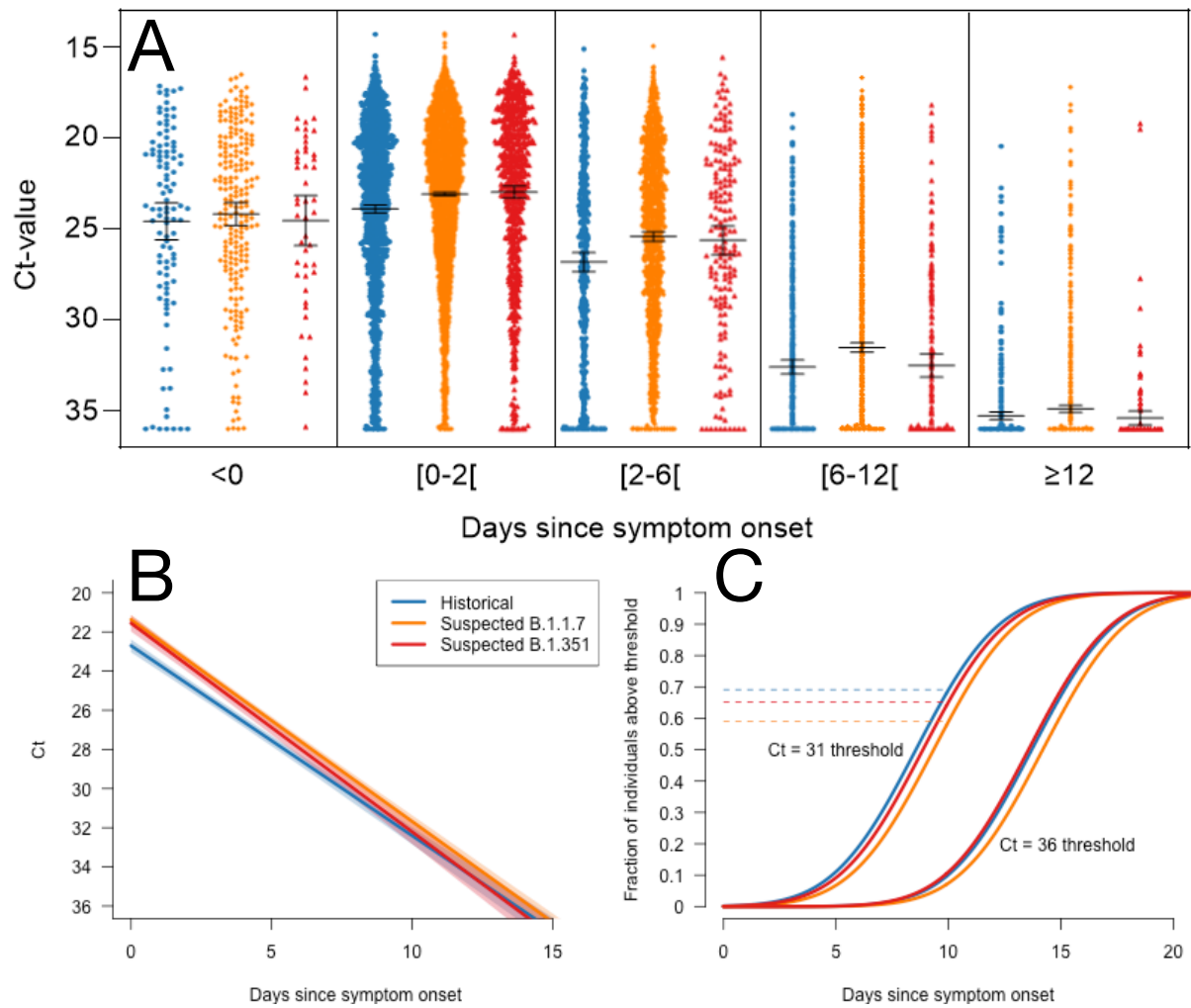
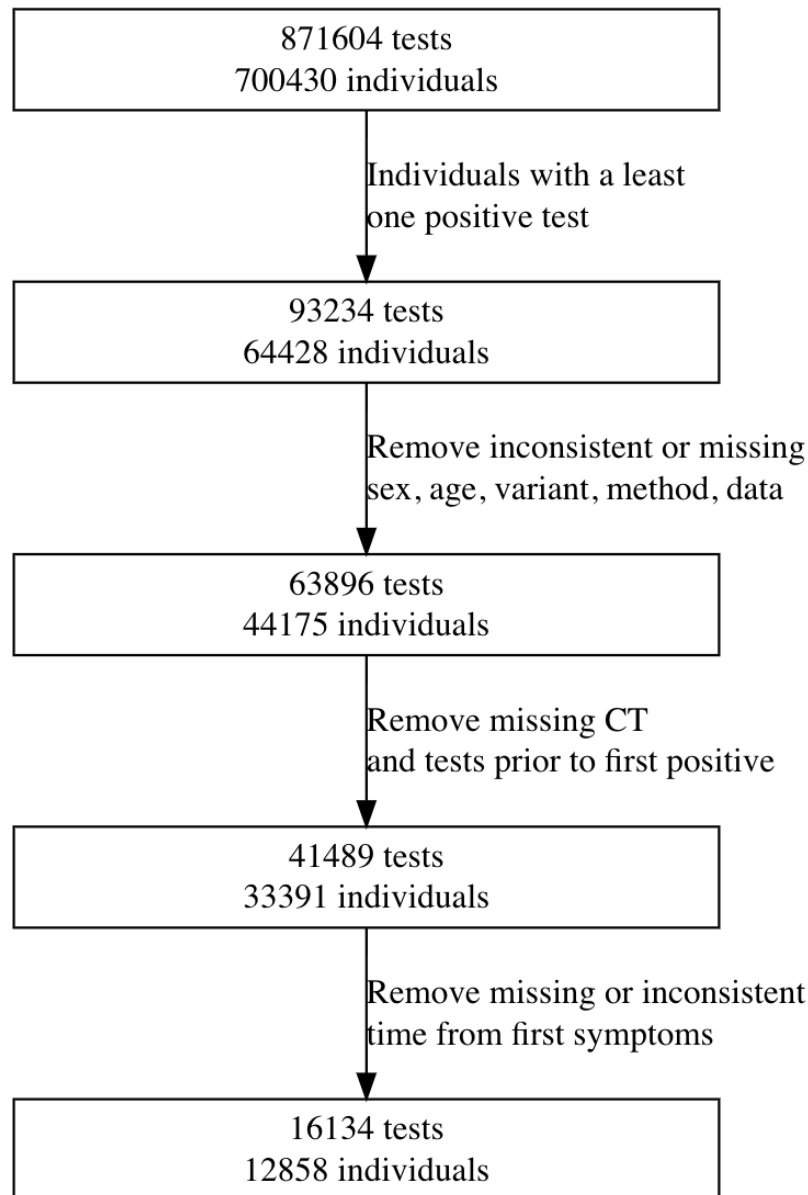
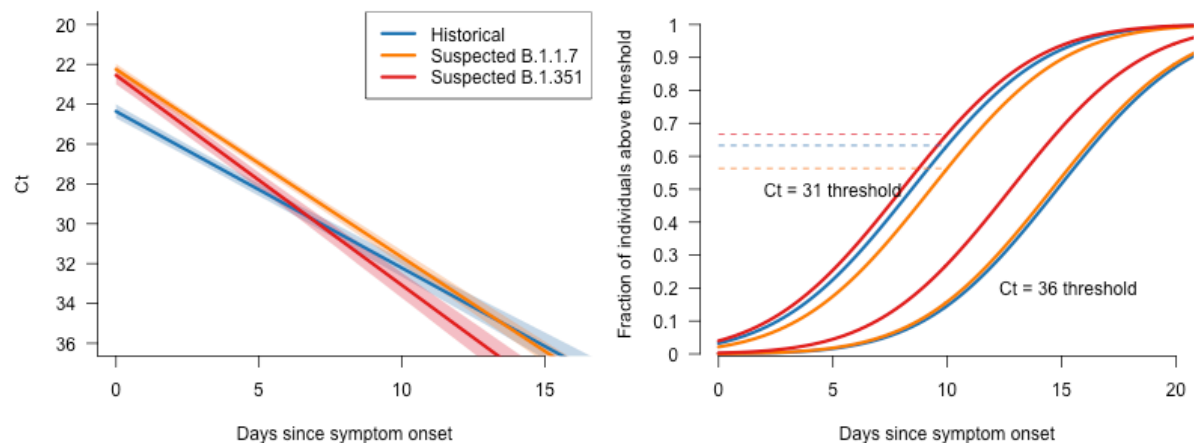


Figure 1: Ct value as a function of time since symptom onset for historical variants, suspected B.1.351 and suspected B.1.1.7. A. Ct value as a function of time since symptom onset categories in the data. B. Prediction of the linear model, with confidence intervals as shaded regions. C. Distribution of the time from symptom onset to thresholds Ct = 31 and Ct = 36 for each variant, as predicted by the linear model. This is the cumulative distribution function of the normal distribution whose mean is the predicted mean time to each threshold for each variant, and standard deviation the standard deviation of the random effect representing the inter-individual variability ($sd = 2.9$). The dashed horizontal lines show the fraction of individuals no longer shedding infectious virus 10 days after symptom onset, the recommended duration of self-isolation in April 2021 in France.



Supplementary Figure 1: Flow chart of the data cleaning. We retained all individuals with at least one positive nasopharyngeal swab ($N = 93,234$). A positive test was defined as a test with at least one PCR with a cycle threshold (Ct) value below 36 (recommendation of the *Société Française de Microbiology*). We retained all individuals with present information on sex, age, variant, PCR method and, for individuals with multiple tests, we retained only those who had consistent information on sex, age, or variant at these tests ($N = 63,896$). We retained all tests with non-missing Ct value on the RdRp gene (the most sensitive assay), all done with the Eurobio EBX-041 method (EurobioPlex SARS-CoV-2-Multiplex), and all tests at or after the first positive test ($N = 41,489$). Finally, we retained all individuals with consistent time from first symptoms data ($N = 16,134$); some of the individuals with multiple tests had a set of self-reported symptom dates not compatible with a unique date of symptom onset, as explained in more details below.



Supplementary Figure 2: Ct value as a function of time since symptom onset for historical variants, suspected B.1.351 and suspected B.1.1.7 for the Ct value of the PCR targeting the N gene. Left panel, prediction of the linear model, with confidence intervals as shaded regions. Right panel, distribution of the time from symptom onset to thresholds Ct = 31 and Ct = 36 for each variant, as predicted by the linear model. This is the cumulative distribution function of the normal distribution whose mean is the predicted mean time to each threshold for each variant, and standard deviation the standard deviation of the random effect representing the inter-individual variability ($sd = 4.6$). The dashed horizontal lines show the fraction of individuals no longer shedding infectious virus 10 days after symptom onset, the recommended duration of self-isolation in April 2021 in France.

Names	Effect	[95 % CI]	p-value
Intercept	22.7	[22.4; 23]	-
Time since symptom onset	0.971	[0.926; 1.02]	< 1e-16
Variant B.1.351	-1.15	[-1.57; -0.697]	< 1e-16
Variant B.1.1.7	-1.33	[-1.59; -1.07]	
Age [0-9]	1.76	[0.982; 2.54]	< 1e-16
Age 10-19	0.704	[0.338; 1.11]	
Age 20-29	0.285	[-0.0114; 0.601]	
Age 30-39	0.309	[0.0181; 0.619]	
Age 50-59	-0.308	[-0.635; 0.0189]	
Age 60-69	-0.0862	[-0.537; 0.359]	
Age 70-79	-0.395	[-0.944; 0.226]	
Age 80-89	-0.848	[-2.08; 0.33]	
Age 90+	0.254	[-1.8; 2.24]	
Time × Variant B.1.351	0.0952	[0.0184; 0.157]	0.000414
Time × Variant B.1.1.7	0.0602	[0.0147; 0.1]	
Time × Age 0-9	-0.16	[-0.306; -0.00743]	1.76e-11
Time × Age 10-19	0.0443	[-0.0313; 0.114]	
Time × Age 20-29	0.0818	[0.0242; 0.133]	
Time × Age 30-39	-0.0092	[-0.0618; 0.0428]	
Time × Age 50-59	0.00329	[-0.0619; 0.0618]	
Time × Age 60-69	-0.129	[-0.2; -0.056]	
Time × Age 70-79	-0.222	[-0.317; -0.137]	
Time × Age 80-89	-0.226	[-0.434; -0.0287]	
Time × Age 90+	-0.431	[-0.735; -0.0897]	

Supplementary Table 1: Estimated fixed effects on Ct values (negatively correlated with viral load), 95% confidence intervals, and p-values, for the main model. Time is in days since symptom onset. For variants, the reference category is historical variants; for age, the reference category is age 40 to 49.

Names	Effect	[95 % CI]	p-value
Intercept	24.4	[24; 24.7]	-
Time since symptom onset	0.786	[0.733; 0.835]	< 1e-16
Variant B.1.351	-1.81	[-2.32; -1.32]	< 1e-16
Variant B.1.1.7	-2.11	[-2.38; -1.81]	
Age [0-9]	1.47	[0.487; 2.27]	1e-11
Age 10-19	0.944	[0.491; 1.35]	
Age 20-29	0.199	[-0.166; 0.565]	
Age 30-39	0.378	[0.0214; 0.753]	
Age 50-59	-0.201	[-0.584; 0.21]	
Age 60-69	-0.177	[-0.631; 0.314]	
Age 70-79	-0.186	[-0.965; 0.513]	
Age 80-89	-0.263	[-1.53; 0.997]	
Age 90+	1.37	[-0.704; 3.92]	
Time × Variant B.1.351	0.268	[0.197; 0.333]	< 1e-16
Time × Variant B.1.1.7	0.157	[0.117; 0.196]	
Time × Age 0-9	-0.0879	[-0.239; 0.102]	0.0005
Time × Age 10-19	-0.00847	[-0.0775; 0.0644]	
Time × Age 20-29	0.0675	[0.0127; 0.12]	
Time × Age 30-39	-0.00466	[-0.0587; 0.0496]	
Time × Age 50-59	-0.00706	[-0.0696; 0.0566]	
Time × Age 60-69	-0.0962	[-0.177; -0.0241]	
Time × Age 70-79	-0.0934	[-0.199; 0.0183]	
Time × Age 80-89	-0.157	[-0.358; 0.0262]	
Time × Age 90+	-0.218	[-0.636; 0.144]	

Supplementary Table 2: Estimated fixed effects on Ct values (negatively correlated with viral load), 95% confidence intervals, and p-values, for the main model applied to the Ct value of the PCR targeting the N gene instead of the RdRp gene. Time is in days since symptom onset. For variants, the reference category is historical variants; for age, the reference category is age 40 to 49.

Names	Effect	[95 % CI]
Intercept	25.5	[25.3; 25.7]
Time since first positive	1.19	[1.15; 1.23]
Variant B.1.351	-1.41	[-1.63; -1.16]
Variant B.1.1.7	-1.17	[-1.32; -1.03]
Age [0-9]	1.85	[1.58; 2.14]
Age 10-19	0.793	[0.618; 0.997]
Age 20-29	0.343	[0.165; 0.526]
Age 30-39	0.147	[-0.0437; 0.314]
Age 50-59	-0.375	[-0.569; -0.192]
Age 60-69	-0.595	[-0.836; -0.366]
Age 70-79	-0.526	[-0.823; -0.201]
Age 80-89	-0.782	[-1.16; -0.383]
Age 90+	-1.04	[-1.63; -0.426]
Asymptomatic then sympt.	-0.627	[-0.853; -0.406]
Symptomatic then asympt.	-0.319	[-0.539; -0.105]
Symptomatic	-0.951	[-1.08; -0.833]
Symptoms unknown	0.633	[-0.272; 1.68]
Time × Variant B.1.351	0.0974	[0.042; 0.158]
Time × Variant B.1.1.7	0.0464	[0.0152; 0.0782]
Time × Age 0-9	0.321	[0.201; 0.432]
Time × Age 10-19	0.035	[-0.0236; 0.0894]
Time × Age 20-29	0.0449	[-0.00734; 0.0936]
Time × Age 30-39	0.05	[-0.00637; 0.102]
Time × Age 50-59	-0.0813	[-0.131; -0.031]
Time × Age 60-69	-0.108	[-0.171; -0.0485]
Time × Age 70-79	-0.344	[-0.413; -0.275]
Time × Age 80-89	-0.483	[-0.559; -0.414]
Time × Age 90+	-0.284	[-0.415; -0.149]

Supplementary Table 3: Estimated fixed effects on Ct values (negatively correlated with viral load), 95% confidence intervals for the regression model on the more complete dataset (41,489 tests representing 33,391 individuals). Time is in days since first positive test instead of time since symptom onset. For variants, the reference category is historical variants; for age, the reference category is age 40 to 49.