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Letter to the Editor

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

We read with interest the article by Tang et al. on the multiple introductions of variant B.1.351 into the UK.¹ As SARS-CoV-2 variants of concern rapidly spread internationally, it is important to

know if increased transmissibility²⁻⁴ and virulence⁵ is associated with higher viral load to understand pathogenesis and adapt if necessary the duration of isolation of infected individuals. When comparing viral load across variants, controlling for time since symptoms is key, since individuals infected by a variant with faster epidemiological growth will on average be captured earlier in in-

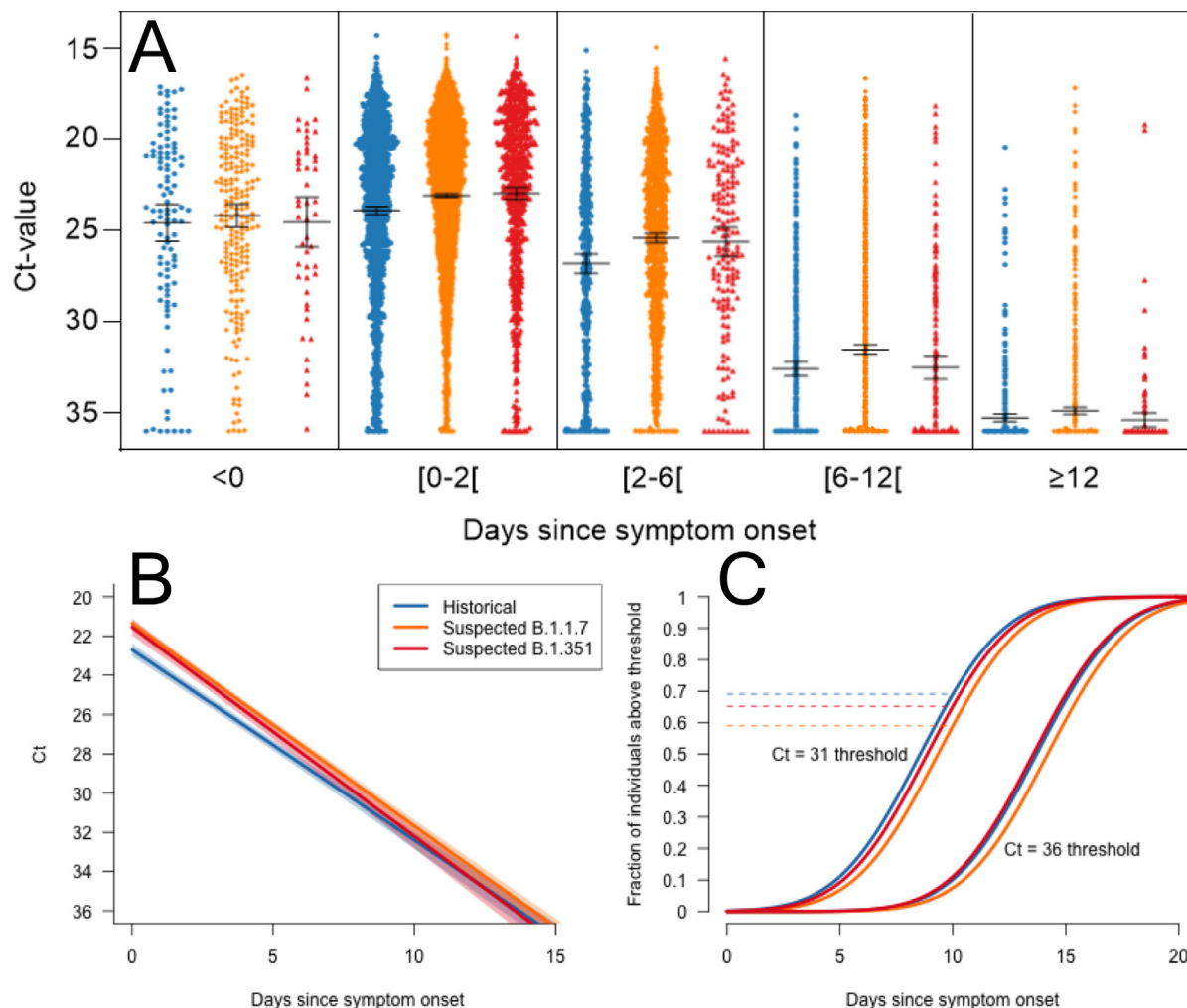


Fig. 1. Ct value as a function of time since symptom onset for historical variants, suspected B.1.351 and suspected B.1.1.7. A. Ct value as a function of time since symptom onset categories in the data. B. Prediction of the linear model, with confidence intervals as shaded regions. C. Distribution of 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.

fection⁶. Studies controlling for time since symptoms, and with longitudinal follow-up of individuals are lacking. 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 (Alpha, VOC-202012/01 or 501Y.V1, first detected in England in September 2021) and B.1.351 (Beta, 501Y.V2) to previous strains.

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 (Supplementary Fig. 1). Most individuals had one test ($N = 10,225$), 2121 individuals had two tests and the rest ($N = 512$ individuals) had three or more tests (Table 1). We conducted the main analysis on the Ct value combining the two Ct values obtained with two primers targeting the RNA-dependent RNA polymerase (RdRp) gene. 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). Symptom onset dates were self-reported. We used a censored mixed-effects linear regression⁷ describing Ct value 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 interactions between time and variant, and time and age (excluding the non-significant interaction between variant and age, $p = 0.31$).

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 (Fig. 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 (Fig. 1C).

We based the main analysis 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 B.1.351) (Supplementary Table 2, Supplementary Fig. 2). We also 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), and in addition, individuals declaring symptoms at all their tests had a larger viral load than asymptomatic individuals (-0.95 , CI [-1.1 , -0.83]).

Both B.1.1.7 and B.1.351 variants conferred a higher viral load at symptom onset at all ages. The main strengths of our study are the control for time since symptoms, which improves the comparison between historical strains and variants (removing potential confounders due to different epidemiological dynamics of

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, B.1.351 and B.1.1.7 variants.

Strain	Sex		Age category						Time from symptom onset (days)						Number of tests						
	N	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.1.17	11,496	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

each variant⁶), and the large number of tests for both B.1.1.7 and B.1.351 variants. A limitation is that variant assignment is based on PCR screening; he 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 indicated that the vast majority of viruses with substitution N501Y and spike deletion 69–70 are B.1.1.7.⁸ 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%,⁸ implying 96% of the suspected B.1.351 are true B.1.351 if only clades B.1.351 and P.1 carried N501Y without del69-70. The evidence presented here from thousands of PCR tests broadly agrees with results from densely sampled trajectories of seven individuals infected with B.1.1.7, showing that 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 .⁹ 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.¹⁰ 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. 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 potential epidemiological consequences.

Declaration of Competing Interest

JG has worked as consultant for ROCHE Company.

CRediT authorship contribution statement

Design: FD, FB, with feedback from all authors Data collection: GC, MB, JA, JMG Data cleaning: FD, FB Analyses: FB Wrote the letter: FB with feedback from all authors.

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