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RESEARCH ARTICLE

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Variant-specific SARS-CoV-2 within-host kinetics

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Abstract

Since early 2021, SARS-CoV-2 variants of concern (VOCs) have been causing epidemic rebounds in many countries. Their properties are well characterized at the epidemiological level but the potential underlying within-host determinants remain poorly understood. We analyze a longitudinal cohort of 6944 individuals with 14 304 cycle threshold (*Ct*) values of reverse-transcription quantitative polymerase chain reaction (RT-qPCR) VOC screening tests performed in the general population and hospitals in France between February 6 and August 21, 2021. To convert *Ct* values into numbers of virus copies, we performed an additional analysis using droplet digital PCR (ddPCR). We find that the number of viral genome copies reaches a higher peak value and has a slower decay rate in infections caused by Alpha variant compared to that caused by historical lineages. Following the evidence that viral genome copies in upper respiratory tract swabs are informative on contagiousness, we show that the kinetics of the Alpha variant translate into significantly higher transmission potentials, especially in older populations. Finally, comparing infections caused by the Alpha and Delta variants, we find no significant difference in the peak viral copy number. These results highlight that some of the differences between variants may be detected in virus load variations.

KEYWORDS

ddPCR, SARS-Cov2, variant of concern, viral dynamics, within-host

1 | INTRODUCTION

SARS-CoV-2 "variants of concern" (VOC) correspond to lineage that causes phenotypically different infections from "historical" lineages with increases in contagiousness[1–5] and virulence.[1,6,7] Because of the deadly epidemic rebounds they caused, they are closely monitored through full genome sequencing but also targeted reverse-transcription quantitative polymerase chain reaction (RT-qPCR) screening. The latter is less precise than the former but more affordable, allowing for wider testing.[8] Those assays yield a quantitative value, the cycle threshold (*Ct*), which is often used as a proxy for the amount of virus genetic material,[9,10] although this metric should be handled with care for coronaviruses.[11]

Many studies analyzed the epidemiology of VOCs but their within-host properties are less clear. Indeed, cross-sectional studies alone are not sufficient to characterize potential variants impacts on virus dynamics due to identifiability issues.[12–14] Still, a few cross-sectional studies have reported lower *Ct* values for Alpha than for "historical" infections[1,15] suggesting that VOCs could be causing infections with higher virus loads. Therefore, longitudinal analyses are necessary to better understand the within-host kinetics of SARS-CoV2 variants infections.

The field of within-host kinetics has grown focusing mainly on chronic infections, but some studies consider acute infections.[16] In the case of SARS-CoV-2, several studies used *Ct* values as a proxy for virus load to report temporal variations within individuals, on

longitudinal data from hospitalized patients,[17] health workers,[18] and experimental infections in nonhuman primates.[19] More recently, studies focusing on the effect of the vaccine showed an overall decrease in viral loads among vaccinated infected patients,[20] or a faster viral load decrease,[21,22] although this remains unclear for symptomatic infections.[23] These studies illustrate that viral kinetics reflect some properties of the infection and can explain some of the variations in the detection probability.

Here, we analyze SARS-CoV-2 kinetics in a large number of individuals using linear mixed models, which allows us to explore how virus load dynamics may vary depending on the setting (general population or hospitals) or the variant causing the infection.

2 | MATERIALS AND METHODS

2.1 | Data

This study was approved by the CHU of Montpellier's Institutional Review Board and is registered at ClinicalTrials.gov (no NCT04653844). The data originates from variant-specific RT-qPCR tests performed in France between February 06 and August 21, 2021 on SARS-CoV-2 positive samples,[13,15] from four different kits, following the manufacturer's instructions. In particular, we used synthetic DNA as an internal control.

The multiplex assays use probes targeting variant-specific mutations (see Table 1), as well as a region in the N virus gene for control purposes. We use the *Ct* of the later probe in our analyses. Therefore, we consider the infecting virus as "historical lineage" if it does not possess any of the key mutation associated with VOCs. The variant-specific qPCRs results were validated internally using next-generation sequencing.

Given the specificity of each assay used, different formatting steps were used. In particular, the initial IDS1 test designed to distinguish between the historical lineages and the Alpha VOC may increase the proportion of the latter VOC for high *Ct* values. Further details are shown in the flow diagram in Figure 1 and can be found in earlier studies.[8,13,15]

2.2 | Digital droplet PCR

Using *Ct* measures as a proxy for virus load has several limitations, especially in the case of coronaviruses.[11] Here, we do not attempt to equate the two but rather assume that temporal variations in *Ct* values are associated in changes in infectiousness.

To further investigate the biological significance of *Ct* values, we analyzed samples from infections by a known virus lineage, that is, historical or VOC, using both a variant-specific PCR and a digital droplet PCR (ddPCR). More precisely, we used the SARS-CoV-2 droplet digital PCR (ddPCR) Kit (BioRad), which has two couples of primers targeting regions N1 and N2 in the virus, and the cellular human RNAse P for internal control.

2.3 | Statistical analyses

2.3.1 | Linear mixed models

We used a linear model to study the potential link between the *Ct* value of the screening test and the number of virus copies obtained using ddPCR, using virus lineage and test assay as a cofactor. The results of the statistical model were used to convert *Ct* values from all assays into a number of virus copies.

We analyzed the longitudinal data of number of virus copies (or *Ct* values for IDS1) with linear mixed models and used the R package lme4[24] to fit the restricted maximum likelihood parameters to the data. The response variable was the number of virus copies (or the *Ct* value for IDS1), and we included two random effects on the individual and on the region of sampling.

To select which additional effects to include in the linear mixed model, we compared models with all possible parameters combinations listed in Table 2. The best model was chosen based on the Akaike information criterion (AIC).[26]

We verified that models with $\Delta AIC < 2$ were qualitatively identical to the model with the best AIC.[26] We also verified that the censored data points (i.e., the *Ct* values above the limit of detection, which was set at 37, or the viral copies number below 10 000 copies/ml) did not have a significant impact on the results by

TABLE 1 Summary of the assays used to screen for variants of concerns (VOCs) among positive tests

Assay	Detailed name	Targets	Variants
IDS1	ID™ SARS-CoV-2/UK/SA variant Triplex (ID solution)	N501Y, Δ69–70	WT/δ versus α versus β/γ
IDS2	ID™ SARS-CoV-2/N501Y/E484K Quadruplex (ID solution)	N501Y, E484K	WT/δ versus α versus β/γ
IDS3	ID™ SARS-CoV-2/VOC evolution Pentaplex (ID solution)	L452R, E484K, E484Q	WT/α versus β/γ versus δ
Perkin	VariantDetect™ SARS-CoV-2 RT-PCR (PerkinElmer)	L452R, E484K, E484Q	WT/α versus β/γ versus δ

Note: WT stands for wild type, that is historical lineages.

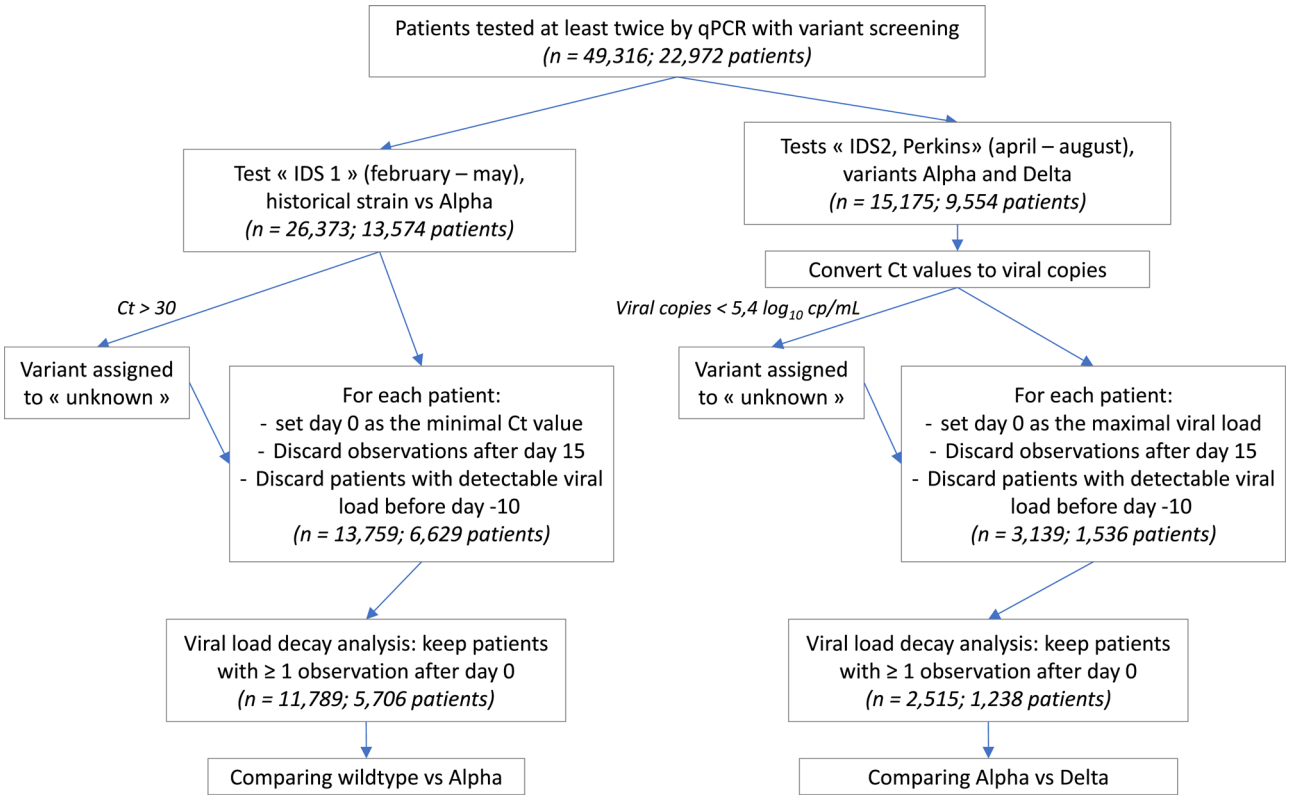

FIGURE 1 Data set formatting steps. *n* indicates the number of tests, that is, *Ct* values, analyzed. For the IDS1 assay, the analyses were performed directly on the *Ct* values because the provider did not have any remaining tests to use with the ddPCR calibration. Furthermore, the assessment of the virus lineage (i.e., wild type or variants of concern) was only performed for tests with *Ct* values lower or equal than 30. For results obtained using the IDS2 and Perkin assays, *Ct* values were converted into viral genome copies before subsequent analysis and the assessment of the virus lineage was only performed for tests with more than $5.4\log_{10}$ copies/ml

TABLE 2 Effects included in the models being tested

Effect	Values	Details
Virus strain	Historical, Alpha, Delta	Variant screening test result
Day	0–15 days	Day 0 being that with the lowest *Ct* value in an individual
Hospitalization	Yes or No	If the patient was sampled at least once in a hospital
Age	5–97	Age of the patient
Variant reproduction number	0.7–1.8	Average number of secondary infections caused by an infected person at a given date,[25] stratified by region
Delay between 1st and 2nd test	1–15 days	Proxy for the bias in the time of first test, assuming 2nd test is done 7 days after symptoms onset
Vaccine coverage	0%–100%	Vaccine coverage at the time of infection for the corresponding age class
Interaction between day and each effect		This represents the impact of each effect on the viral copy number decay after peak
Interaction between the age and virus strain		This represents the differential impact of the variant on the viral copy number peak in function of the age

computing all the linear mixed models selected by a $\Delta AIC < 2$ with a censored effect using the lmec R package.

Differences in viral copies between populations from the linear model outputs were statistically assessed using the Tukey adjustment and the emmeans R package.

2.3.2 | Variant specific reproduction number

We first calculated the global epidemic reproduction number in each French region using hospital admission data.[27] We then adjusted this number by using the estimated relative proportion of each variant

among the daily infections caused,[5,8,15] and the mean transmission advantage computed by an independent study.[28]

2.3.3 | Transmission potential

We used the infectiousness profile estimated from the data of He et al.[29] corrected by Marks et al.[30] that is, a shifted Gamma distribution, with shape 97.19, rate 3.72, and shift 25.63.

This analysis being restricted to one test (IDS1), we studied the correlation between the *Ct* value and the instantaneous infectiousness, that is, the infectiousness profile density.

We then used this mapping to infer a transmission potential, which can be seen as a proxy for the basic reproduction number.[31] Using the outputs of our model capturing within-patient dynamics, we integrated the infectiousness obtained from the *Ct* values from Day 0 to Day 15.

3 | RESULTS

3.1 | From *Ct* values to number of virus copies

For a given RT-qPCR assay, we found a log-linear relationship between the *Ct* value and the absolute number of viral copies measured by ddPCR (Figure 2). Compared to the reference (i.e. IDS2), IDS3 yielded a *Ct* value 1.96 lower (Student *t*-test, Tukey adjustment: $p < 10^{-4}$), and Perkin a Ct value 6.9 higher ($p < 10^{-4}$). For the Perkin assay, we also detected a significant effect of the variant on the *Ct*

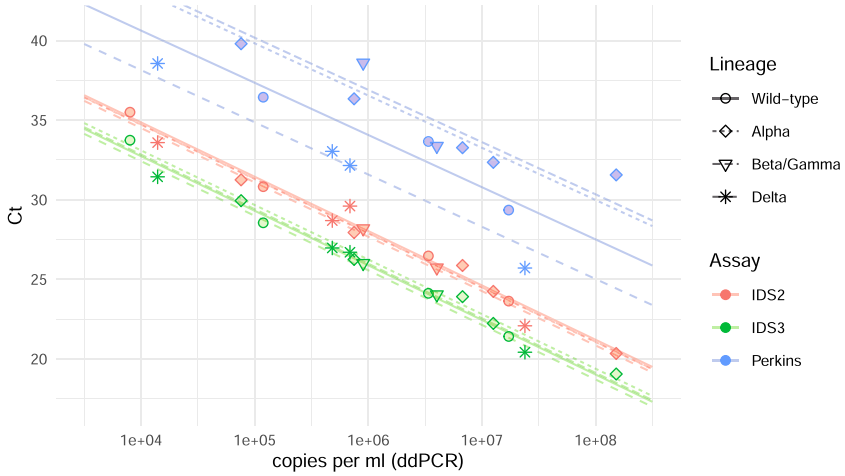

FIGURE 2 *Ct* value as a function of SARS-CoV2 copy number. The shape indicates the virus lineage and the color variant screening assay used to obtain the *Ct* value for the control probe targeting the N gene. Virus copy number was estimated using a droplet digital polymerase chain reaction targeting the N gene

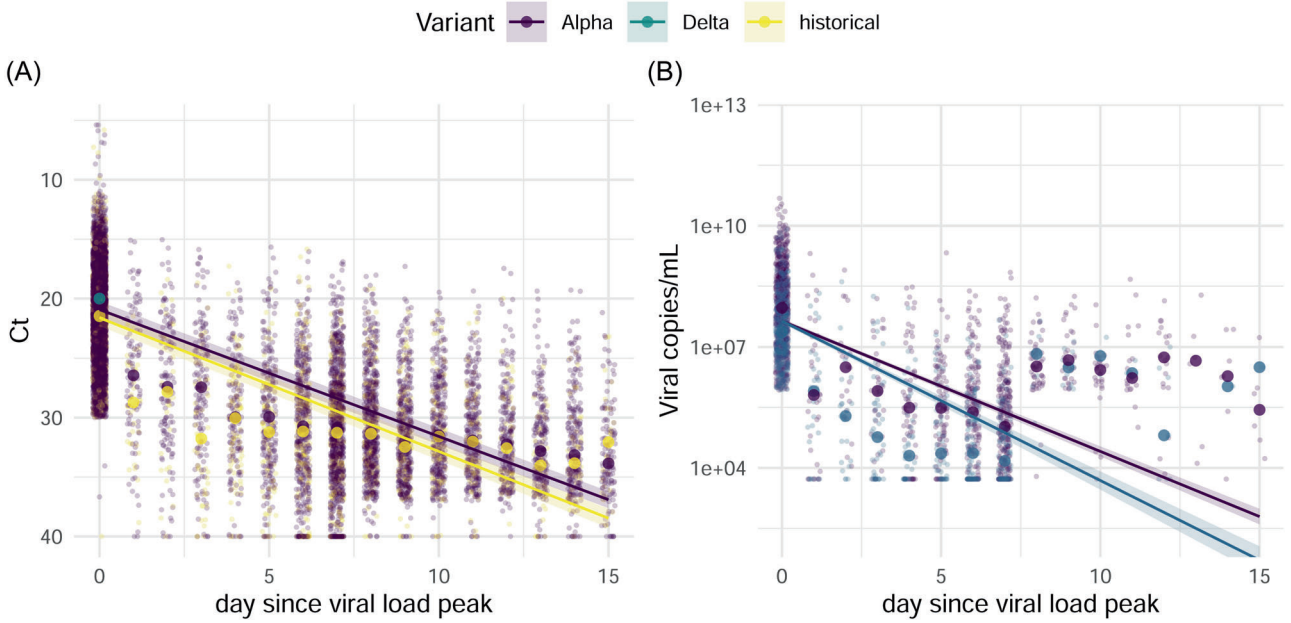

FIGURE 3 Within-host longitudinal *Ct* data as a function of the virus lineage. The dots represent the observed values. The bold dots represent the median value for each day and each strain. The lines represent the linear model for an average patient (median age, nonhospitalized). (A) Model with *Ct* values of historical lineages versus the Alpha variant. (B) Model of virus copies per milliliter of Alpha versus Delta variant. Both models were set approximately on the same scale on the *y*-axis

TABLE 3 Properties of the longitudinal datasets: (i) based on the ISD1 assay (historical lineages vs. alpha variant), the data contain 12 536 *Ct* values from 6064 individuals, and (ii) based on IDS2, Perkin or IDS3 assays (alpha vs. delta variants), the data contain 2751 *Ct* values from 1239 individuals

Variable	Value	Historical strains versus alpha variant model Median (IQR) or *n* (%)	Alpha versus delta variant model Median (IQR) or *n* (%)
Sampling context	*General population (ref)*	5706 (94%)	1263 (93%)
	hospital	358 (6%)	92 (7%)
Age		41 (25–58) y.o.	35 (23–54) y.o.
Follow up duration		8 (6–10) days	6 (5–7) days
Date of first sampling (in 2021)		March 9 (February 20–March 22)	May 5 (April 21–July 21)
Lineage	*Wildtype*	1211 (20%) *(ref)*	6 (0.4%)
	Alpha	4495 (74%)	849 (63%) *(ref)*
	Beta/Gamma/Eta	358 (6%)	110 (8%)
	Delta	0	390 (29%)
Samples per individual	2	5686 (93%)	1313 (97%)
	>2	378 (7%)	42 (3%)
Administrative region	*Ile-de-France*	3863 (64%)	676 (50%)
	Normandie	659 (11%)	181 (13%)
	Hauts-de-France	612 (10%)	142 (10%)
	PACA	273 (4%)	204 (15%)
	Other	657 (11%)	151 (12%)
Screening assay	*IDS1*	12 536	0
	IDS2	0	1928 (70%)
	Perkin	0	824 (30%)
	IDS3	0	1 (<1%)

value. For the same number of virus copies, we found a ΔCt of 5.0 between samples originating from an infection by a Delta or an Alpha variant ($p < 10^{-4}$).

3.2 | Historical lineages versus the alpha variant

After formatting the database for the IDS1 assay (Figure 1), we identified 12,536 suitable samples (Table 3). Due to the limited number of observations, we removed patients infected lineages consistent with the Beta/Eta/Gamma VOCs.

To analyze the virus load kinetics, we inferred linear mixed models and selected the one with the lowest AIC. The estimated values of the model are shown in Table 4.

The linear mixed model revealed significant differences in *Ct* values dynamics between the historical lineages and the Alpha VOC (Figure 3A). First, compared to historical lineages infections, the peak *Ct* appeared to decrease with age for infections caused by the Alpha VOC (Table 4). Overall, for the French age structure, the peak *Ct* was significantly lower (−0.67 *Ct* [0.87, −0.46]). Furthermore, in infections caused by the Alpha VOC, the rate of *Ct* increase over the infection was lower. As a result, 7 days after the viral copy number peak, the *Ct* difference was larger (−1.08 *Ct* [−1.32, −0.85]). Finally, we also observed a significant impact of the hospitalization status, with a lower peak *Ct* value.

We also used a survival analysis approach to measure the period during which individuals have a *Ct* below 30 which is commonly considered as a threshold for infectivity. The results are detailed in the appendix. We observed that the median infectious period depends mostly on the individuals' age, and on the infecting strain, with individuals infected by the Alpha variant having a median infectious period 0.7 days longer than the ones infected by the historical strains (Figure S1).

3.2.1 | Alpha transmission potential advantage

To further investigate the implications of these results at the population level, we performed a mapping between the daily infectivity and the daily *Ct* value after its peak for the wild-type

TABLE 4 Linear mixed model parameters estimates (Historical lineages vs. Alpha variant)

Predictor	Estimate	95% CI
Intercept	**24.9**	**(24.1, 25.7)**
Day	**1.25**	**(1.20, 1.30)**
Age	−0.0049	(−0.011, 0.001)
No	Ref	—
Hospitalization ***yes***	**−1.36**	**(−1.75, −0.97)**
Delay between first and second test	**−0.40**	**(−0.43, −0.37)**
Day: age	**−0.0029**	**(−0.0036, −0.0022)**
Historicalday: strain	Ref	—
Alpha	**−0.059**	**(−0.097, −0.021)**
Historicalage: strain	Ref	—
Alpha	**−0.016**	**(−0.020, −0.011)**

Note: Bold rows correspond to estimates with $p < 0.05$. The notation a:b indicates an interaction between factors a and b. CI stands for "confidence interval." The random effect of the patients on the intercept has a standard deviation of 2.075 (1.95, 2.19), the random effect of the region on the intercept has a standard deviation of 1.051 (0.61, 1.72) and the residues have a standard deviation of 3.89 (3.82, 3.96).

strain inferred from the linear model. The resulting significant correlation (Figure 4A, $R^2 = 0.95$) supports a linear relationship between *Ct* and infectiousness.

We used this mapping between *Ct* values and infectivity to study transmission potential differences between lineages. We found that the advantage of the Alpha VOC over the historical strain was more pronounced in countries with older populations (Figure 4B).

3.3 | Alpha versus delta variant

We then analyzed the data which involved *Ct* values from three other assays that we were able to convert into virus copy numbers (see Section 2 and Figure 2). In the following, we use a log base 2 relationship with time since peak of viral genome copies to compare the orders of magnitude with the previous results.

Infections consistent with viruses from Beta/Gamma/Eta lineages were too rare to be analyzed and removed them from the data set. Overall, we were able to compare infections caused by the Alpha or the Delta variant by analyzing the remaining 2515 samples (Table 3). Compared to the previous data set, patients were slightly younger (median age 35 vs. 41) and the follow-up duration was shorter (median 6 vs. 8 days). This latter difference was corrected by the variable taking into account the delay between first and second test.

The best model according to the AIC criterion is detailed in Table 5 and the dynamics of the number of viral genome copies is shown in Figure 3B. On 15 out of 17 models with a $\Delta AIC < 2$, we found no significant difference between the kinetics of the infections caused by the Alpha and the Delta VOC on the peak viral copy number. However, we found a significant difference on the decay rate on 13 models.

To make sure that this result was not due to confounding factors, we included several covariates in our analysis which revealed a strong effect of the sampling date, which could interfere with the variant effect (since the Delta VOC rapidly replaced the Alpha VOC). The vaccine coverage in the population, which was used a proxy for the probability that the individual was vaccinated, as well as the delay between first and second test, measuring behavioral differences, were retained as a cofactor in the best linear model. Furthermore, the variant-specific reproduction number $R(t)$, estimated at the regional level in France was also retained as a significant covariate, which is consistent with previous observations,[13,14] although the effect was not statistically significant.

Finally, we also ran a survival analysis as a second approach, and observed a similar trend, with individuals infected by the Alpha variant having a median infectious period 1.75 days longer than the ones infected by the Delta variant (Figure S2).

4 | DISCUSSION

Understanding the within-host kinetics of SARS-CoV-2 infections yielded original insights on infection virulence,[17] or efficiency of screening strategies.[18] We analyzed a large national data set of longitudinal RT-qPCR *Ct* values to test the hypothesis that epidemic rebounds associated with SARS-CoV-2 variants could be linked to specificites in their within-host kinetics.

A linear mixed model indicated that infections caused by SARS-CoV-2 Alpha variant have higher virus loads, with a significant age dependence. Furthermore, the temporal decrease in virus load was found to be slower when infections were caused by Alpha instead of the historical lineages. The results are consistent with results from a different cohort in France.[32]

To further investigate the consequences of these variations in within-host kinetics at the epidemiological level, we assumed a linear correlation between *Ct* value and daily infectiousness, which is consistent with an earlier study[33] and confirmed by a modeling approach.[34] Translating the estimated Ct kinetics into transmission potential profiles revealed that the high viral copy number observed in Alpha VOC infections were consistent with a 25% increase in transmission potential compared to historical strains.

Kinetics of samples collected in hospitals exhibited higher peak viral genome copies (i.e., lower *Ct* values), which is consistent with earlier studies.[17] The results were unaffected by the removal of hospital data from the analysis.

We were unable to convert the *Ct* values from the first assays into number of virus genomes, which precluded us from comparing the Delta variant to the ancestral lineages. Therefore, we limited our comparison of the Delta variant to the infections caused by the

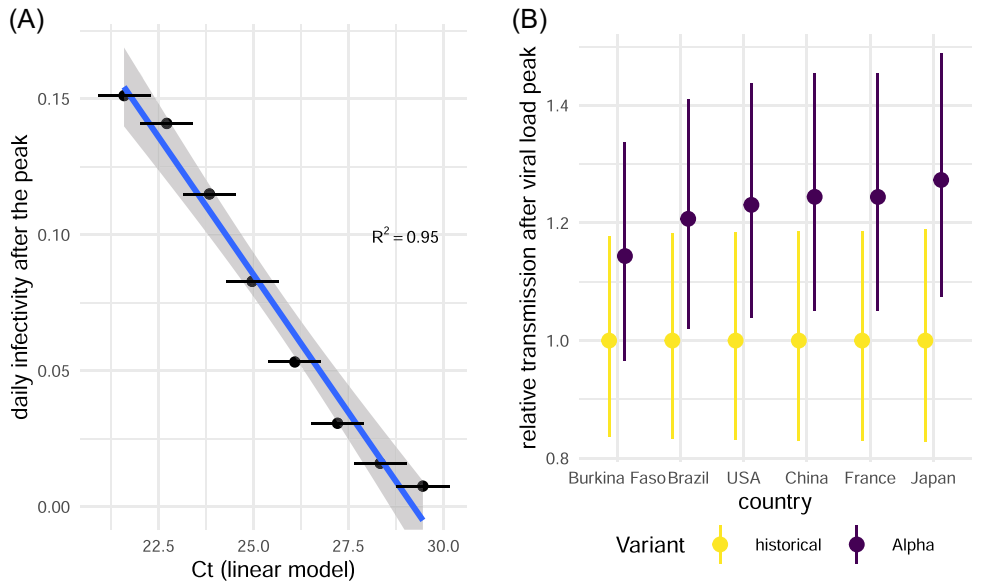

FIGURE 4 Impact of the differential viral genome copies on the transmissibility. (A) Relationship between infectivity and *Ct*, after the viral genome copies peak, for the historical strain. (B) The linear model parameters were used, with the demography of each country, to infer the transmission advantage of the variants. The error bars represent the 95% bootstrap quantile

TABLE 5 Linear mixed model parameters estimates (Alpha vs. Delta variant)

Predictor	Estimate	95% CI
Intercept	**20.14**	**(18.9, 21.4)**
Day	**−1.33**	**(−1.42, −1.24)**
Age	**0.024**	**(0.013, 0.034)**
R(*t*) variant specific	0.90	(−0.19, 1.98)
Vaccine coverage	**−0.034**	**(−0.045, −0.023)**
Delay between first and second test	**0.67**	**(0.59, 0.74)**
Day: age	**0.0061**	**(0.0043, 0.0080)**
Day: hospital	**0.12**	**(0.0018, 0.25)**
Alphaday: strain	**Ref**	—
Delta	**−0.24**	**(−0.33, −0.15)**

Note: Bold rows correspond to estimates with $p < 0.05$. CI stands for "confidence interval." The notation a:b indicates an interaction between factors a and b. The random effect of the patients on the intercept has a standard deviation of 1.69 (1.42, 1.91), and the residues have a standard deviation of 3.50 (3.37, 3.64).

Alpha variant. Our models show no difference in the peak of viral copy number, but they detect a faster decrease in infections caused by the Delta variant than in that caused by the Alpha variant. This may appear as counter-intuitive given the latter has a clear transmission advantage over the former.[5,28] This could be explained by the fact that ddPCR itself is limited because it does not count the number of infectious virions.[11] Indeed, experiments suggest that for a given *Ct* value, samples from Delta VOC infections have a higher number of infectious particle than that from Alpha VOC infections.[35] Finally, this result is also consistent with others that find little differences in *Ct* values between infections caused by the Alpha and the Delta VOC.[22]

A limitation of this analysis is that we do not have any indication regarding the date of the infection or of the symptom onset. This uncertainty prevented us from analyzing more mechanistic models with nonlinear mixed-effect models.[17] However, since the nature of the virus causing the infection is unlikely to affect the number of days between infection and screening, we do not expect our assumption that the lowest *Ct* value corresponds to the peak viral genome copies to introduce biases.

Our comparison between the Alpha and Delta VOCs is potentially subject to additional biases. This part of the analysis covers a large period of sampling, with an important increase in the vaccine coverage, and potential behavioral changes. We attempted to correct for those biases by including covariates such as vaccine coverage in the general population, variant reproduction number, or the delay between the first two tests of an infected individual.

The use of age-structured vaccine coverage is a proxy that makes the simplifying assumption that the vaccination does not impact the probability of being infected nor being tested, and therefore the vaccine coverage in the general population would be the same as the one in the samples we studied. However, even if this is a strong assumption, this seems to capture at least part of the effect, and it was found to be significantly impacting the peak viral genome copies, with a lower peak with increasing vaccine coverage.

Moreover, the use of antigenic tests as a first line of screening is likely to have delayed the delay between infection and RT-qPCR testing. Their use increased from 20% to 50% of the total Covid-19 screening tests between May and August in France.[36] We observe that the median delay between the first and the second test (which is usually done 7 days after the symptoms) decreased from 7 to 5 days

during the analysis. We included this variable in the model, and a shorter delay was significantly associated with a smaller peak viral genome copy number. Indeed, we interpret a shorter delay as a first test done later on the infection.

Finally, our statistical analysis does not take into account the fact that *Ct* values beyond 40 are censored, that is, all we know in that case is that the individual cleared the viral genome before the sample date. The statistical tools for linear mixed models with censored effects are less efficient, but we compared the best models obtained without taking into account the censoring effect to the same models with a censoring effect, and most of the models (12/12 for historical strain vs. alpha, 15/17 for alpha vs. delta) yielded similar results both in term of viral copy number peak difference and decay rate. Furthermore, we ran a survival analysis using a Cox model, which also confirmed our observations regarding the impact of each variant on the duration of the time with an infectious viral copy number level.

Overall, our study illustrates the insights that the combination of large screening data and statistical analyses can bring to the understanding of within-patient kinetics and population spread, as illustrated by our comparison between the Alpha variant and ancestral lineages. It also shows the limitations of *Ct* values and the added value of infectivity assays.

AUTHOR CONTRIBUTIONS

Mircea T. Sofonea, Stpéhanie Haim-Boukobza, Bénédicte Roquebert, and Samuel Alizon conceived the project, Sabine Trombert-Paolantoni, Vincent Foulongne, Stpéhanie Haim-Boukobza, and Bénédicte Roquebert collected the data, Baptiste Elie, Mircea T. Sofonea, and Samuel Alizon analyzed the data, Jérémie Guedj provided statistical expertise, Baptiste Elie and Samuel Alizon wrote the first draft the manuscript, and all authors contributed to the final version of the manuscript.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request. Data and code are available on https://gitlab.in2p3.fr/ete/sars-cov2_kinetics

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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