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1 **SARS-CoV-2 variants of concern are associated with**
2 **lower RT-PCR amplification cycles**
3 **between January and March 2021 in France**

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17 **Abstract**

18 SARS-CoV-2 variants raise concern regarding the mortality caused by COVID-19 epidemics. We
19 analyse 88,375 cycle amplification (Ct) values from variant-specific RT-PCR tests performed between
20 January 26 and March 13, 2021. We estimate that on March 12, nearly 85% of the infections were
21 caused by the Alpha variant and that its transmission advantage over wild type strains was between
22 38 and 44%. We also find that tests positive for Alpha and Beta/Gamma variants exhibit significantly
23 lower cycle threshold (Ct) values.

24 **Context**

25 At least three SARS-CoV-2 variants are currently major sources of concern: Alpha from lineage B.1.1.7
26 ([Davies et al., 2021](#); [Volz et al., 2021](#)), Beta from lineage B.1.351 ([Tegally et al., 2021](#)), and Gamma from
27 lineage P.1 ([Faria et al., 2021](#)). Alpha and Gamma variants have been shown to be more contagious ([Davies](#)
28 [et al., 2021](#); [Volz et al., 2021](#); [Faria et al., 2021](#)), while Beta and Gamma seem to evade immune responses
29 ([Tegally et al., 2021](#); [Faria et al., 2021](#)). Although the mechanistic bases are still being investigated, the
30 increased transmissibility could be driven by the N501Y mutation and the $\Delta 69-70$ deletion in the Spike
31 protein ([Davies et al., 2021](#)), where also lies the E484K mutation related to immune escape ([Tegally et al.,](#)
32 [2021](#); [Faria et al., 2021](#)). Current evidence regarding potential differences in cycle threshold (Ct) values
33 are still unclear ([Walker et al., 2020](#); [Faria et al., 2021](#)) as how well they reflect viral loads ([Néant et al.,](#)
34 [2021](#); [Michalakis et al., 2021](#)).

35 In France, using data from 11,916 tests performed on Jan 6 and 7, 2021, a study estimated that 3.3%
36 of the infections were caused by the Alpha variant at that time ([Gaymard et al., 2021](#)). Another study
37 used 40,777 tests performed between Jan 26 and Feb 16, 2021, and estimated that on Feb 16, 55% of the
38 infections were caused by Alpha, Beta, or Gamma variants ([Haim-Boukobza et al., 2021](#)).

39 Here, we estimate the spread of SARS-CoV-2 variants of concern using 123,867 variant-specific RT-
40 PCRs performed in nasopharyngeal (NP) swabs between Jan 26 and Mar 19, 2021 in France and compare
41 Ct values between variants (the dataset and technical specifications are detailed in the Appendix).

42 Alpha variant is dominant

43 Using the same methodology described in [Haim-Boukobza et al. \(2021\)](#) and in the Appendix, we calculated
44 the transmission advantage of each variant compared to the wild type strain after correction for several
45 biases (region, sampling date, assay, and patient age). This inference was performed for individuals from
46 5 to 80 years old) and without the data from hospitals (to avoid sampling delay bias). For Alpha, the
47 transmission advantage was 40% (95% confidence interval, CI: [38,42]%). For Beta-Gamma, the estimate
48 was 28% (95%CI: [27,30]%).

49 We then estimated the proportion of new infections caused by each type of strain on Mar 19, 2021.
50 At a national level, the estimate was 87% for Alpha and 5,4% for Beta/Gamma, but with strong regional
51 heterogeneity (Figure S1).

52 Variants have lower Ct values

53 We analysed tests and for which the strain has been determined from 1 to 89 year old patients with Ct
54 values lower than 30, i.e. 76,745 tests (91% of all the tests with Ct values).

55 We used a multiple linear regression to study variations in Ct values between strains. The covariates
56 were the age, the sampling facility (hospital or city), the sampling date, and the region (including the
57 interaction between the last two). We then performed a F-test of a model including the variant identity
58 as a covariate, in interaction with age, against a model without it. The variant effect was found to be
59 statistically significant while the model explained a small fraction of the Ct variability (adj. $R^2=3.8\%$),
60 which is consistent with these values being highly variable ([Alizon et al., 2021](#)).

61 The virus strain effect was highly significant in the ANOVA (Figure 1). Samples from Alpha variants
62 had a significantly smaller Ct than that from Beta/Gamma (21.8 vs. 22.1). Both had significantly smaller
63 Ct values than wild type strains (22.8) and other variants.

64 The model also indicated a significant decrease of Ct with age, in line with existing data ([Alizon et al.,](#)
65 [2021](#)). Interestingly, this decrease was significantly (more than half) stronger for Alpha, while the inference
66 cannot exclude equivalent slopes for the other variants (note that this trend holds even on the non-Alpha
67 variant subset of Ct values). The sampling date, the sampling region and their interaction were also
68 found to be significant. Samples from hospitals has a slightly higher Ct, likely due to the fact that testing
69 in the general population occurs approximately one week after infection and one week before potential
70 hospitalization. Therefore, hospitalised patients data is likely to reflect an older state of the epidemic.

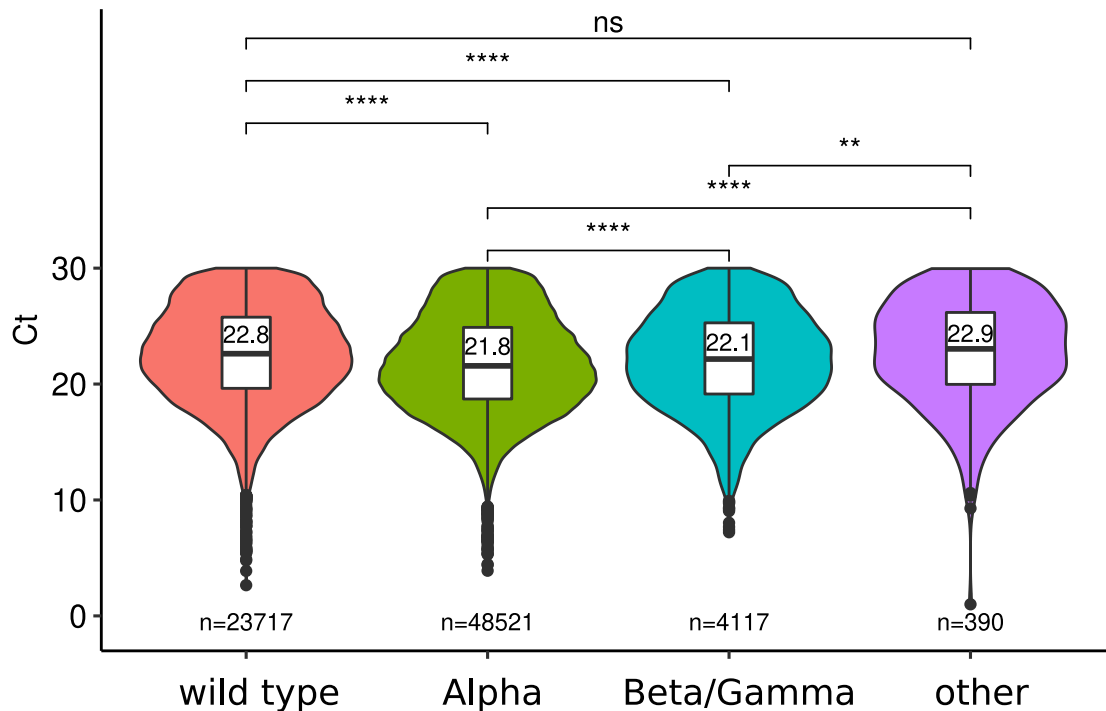


Figure 1: **Cycles threshold (Ct) value for SARS-CoV-2 strains.** Median estimates based on the linear model are shown in the box plot, and number of tests in each class are shown in the bottom of the graph. ‘other’ indicate tests with the $\Delta 69-70$ deletion and without the N501Y mutation. Start indicate the significance level (**** for a p-values strictly lower than 10^{-4} and ** for a p-value of 10^{-4} , ns : not significant).

71 Discussion

72 We show that variant of concern Alpha is now vastly dominant in France compared to wild type strains
 73 (87% vs. less than 10%). Beta or Gamma remain limited (approximately 5.4% of the new infections).
 74 These results are consistent with earlier reports of a marked transmission-advantage of the Alpha variant
 75 (Davies et al., 2021; Volz et al., 2021; Haim-Boukobza et al., 2021; Gaymard et al., 2021).

76 By investigating the RT-PCR Ct values, which can inform us on clinical features of the infection (Néant
 77 et al., 2021; Alizon et al., 2021), we show that infections caused by variants significantly differ from that
 78 caused by wild type strains. That variants are associated with lower Ct values could be an indication of
 79 higher viral load, although care must be taken because of the biology of SARS-CoV-2 (Michalakis et al.,
 80 2021) and of the variability inherent to such values (Alizon et al., 2021).

81 This result contrasts with earlier findings. One study did not find a significant result when comparing
 82 Ct values for tests with or without the S-gene target failure (Walker et al., 2020). However, our results
 83 are based on a variant-specific PCR. Another study on the Gamma variant (Faria et al., 2021) did not
 84 find a significant difference after accounting for the symptom onset to sampling delay. However, their

85 study was performed on a limited number of samples ($n = 147$). Finally, our estimates, based on a large
86 number of interpretable samples with Ct lower than 30, suggest that differences in within-host replication
87 and transcription between Alpha and non-Alpha variants might be lower than previous quantified (Jones
88 [et al., 2021](#)).

89 **Data availability**

90 The data and scripts used for the analysis will be shared upon publication.

91 **Conflict of Interest**

92 None declared.

93 **Funding Source**

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95 **Ethical Approval**

96 This study was approved by the Internal Review Board of the CHU of Montpellier (ClinicalTrial.gov
97 identifier NCT04738331).

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185 Appendix

186 Supplementary methods

187 Dataset

188 We analyse 123,867 variant-specific RT-PCR tests performed in France on the same number of individuals
189 between Jan 26 and Mar 19, 2021. The main assay used was IDTM SARS-CoV-2/UK/SA Variant Triplex
190 (ID SOLUTION) but for 4159 tests (3,4%) performed before Feb 3, 2021 we used the VirSNiP SARS-CoV-
191 2 Spike del+501 (TIB MOLBIOL) assay. The sampling varied between French regions and we excluded
192 from the analysis regions with less than 100 tests. 936 tests were also removed because the sampling region
193 was missing.

194 These tests have probes with 3 targets: a control one in the virus N gene, the $\Delta 69-70$ deletion, and the
195 N501Y mutation. For Alpha variants, both the deletion and the mutation are present. For Beta or Gamma
196 variants, only the N501Y is detected. For VirSNiP assay, it is based on 501 and 69/70 fragments amplified
197 and analyzed with a melting curve using mutation-specific probes, as described earlier ([Haim-Boukobza
198 et al., 2021](#)). As indicated in [Haim-Boukobza et al. \(2021\)](#), the test specificity was confirmed internally
199 using next-generation sequencing.

200 The main cofactors in the analysis were the assay used, the patient age, the sampling date, the sampling
201 region, and the sampling facility (hospitals or city screening).

202 For 119,708 ID SOLUTION tests, we also analyse the cycle threshold value (Ct) of the virus control
203 gene of the assay. Ct values greater than 30 were ignored because they may provide unreliable results
204 regarding the variant-specific probes LoD (Limit of Detection). Indeed, the latter are located in the S
205 gene, which tends to exhibit higher Ct values than the N gene ([Alizon et al., 2021](#)).

206 Linear model for the Ct analysis

207 We performed a type I error for the analysis-of-variance. Our response variable was the Ct value. The
208 main covariate of interest was the strain and it could take 4 values (Alpha, Beta or Gamma, wild type,
209 or other). The other covariates were the age, the sampling facility (hospital or city), the sampling date,
210 and the geographical region. We also considered an interaction between sampling region and date. We
211 used a type-I analysis of variance (ANOVA) and added the strain covariate last. The motivation for this
212 is that with the sequential assumption of the summing of the squares (type I method), the order in which

213 the covariates are tested matters, and, in the case of an uneven sampling, the last one in the list is less
214 likely to be significant. Therefore, our assumption decreases the risk of erroneously attributing observed
215 variance to a variant effect.

216 We used a F-test to determine whether the addition of the strain effect statistically improved the
217 explanation of the data.

218 Generalised linear model to correct for variant sampling bias

219 As indicated in (Haim-Boukobza et al., 2021), for a given variant category (Alpha or Beta/Gamma) we first
220 perform a generalised linear model with a binomial error distribution where the variable of interest is the
221 binary variant variable (with values ‘variant’ or ‘wild type’) and the explanatory variables are the sampling
222 date, the sampling region, and the individual age. We also include an interaction between sampling region
223 and date. We then use the residuals of this model to infer the transmission advantage of the variant.

224 Logistic growth fitting

225 We used the fitted values of a GLM model applied to the data after removing samples from hospitals
226 (the sampling location effect was also obviously removed from the model) to perform the inference of a
227 two-parameter logistic growth kinetic curve: $f(t) = (1 + e^{-\rho(t-\tau)})^{-1}$, where $f(t)$ is the frequency of the
228 variants in the new infections at time t , ρ is the relative growth rate of the variants and τ is the time
229 at which f reaches 1/2. This method is indeed more appropriate to deal with temporal auto-correlation
230 biases in proportion time series (Davies et al., 2021; Volz et al., 2021).

231 The parameter estimation was performed using the `drc` package in R both at the national and the
232 regional level (for regions with at least 1,000 samples). The confidence intervals of the fitted curves rely
233 on those of the estimated date of reaching half proportion of new infections (τ).

234 The unitless estimated transmission advantage is expressed in terms of multiplicative gain in repro-
235 duction number with respect to that of the wild type, such that $\mathcal{R}_{\text{variant}} = (1 + \text{ETA}) \times \mathcal{R}_{\text{wild type}}$. Its
236 calculation was made by solving the Euler-Lotka equation ($\mathcal{R}_{\text{variant}} \int_0^\infty e^{-\rho t} w(t) dt = 1$) assuming a serial
237 interval w following a Weibull distribution with a mean and SD of 4.8 and 2.3 days (Nishiura et al., 2020)
238 and a constant $\mathcal{R}_{\text{wild type}}$ equal to 1. The confidence interval rely on those of the estimated relative growth
239 rate.

240 The estimate of the frequency of variant on Mar 12, 2021, was done by first estimating the proportion p_x
241 of a given variant x compared to the wild type (while ignoring the other variant y) and second performing

242 the same analysis to look at the proportion p_x^T of wild type and x compared to the whole population (x
243 plus y plus wild type). The frequency of variant X was then obtained as $p_x \times p_x^T$.

244 Supplementary figures

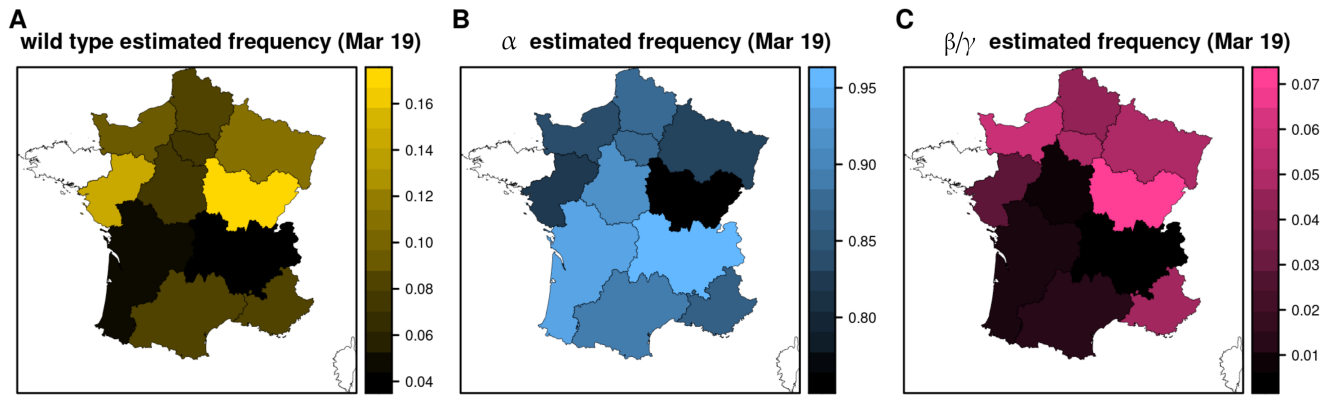


Figure S1: Estimated proportion of new infections caused by A) wild type, B) Alpha variant, and C) Beta or Gamma variants on Mar 12, 2021, in French regions. Regions with insufficient sampling are in white.

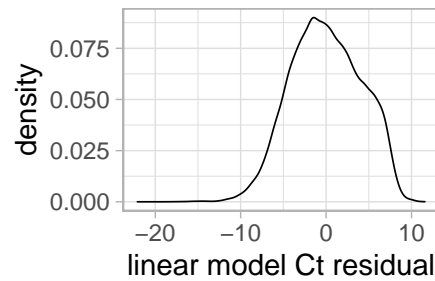


Figure S2: Distribution of the residual values of the multiple regression linear model.

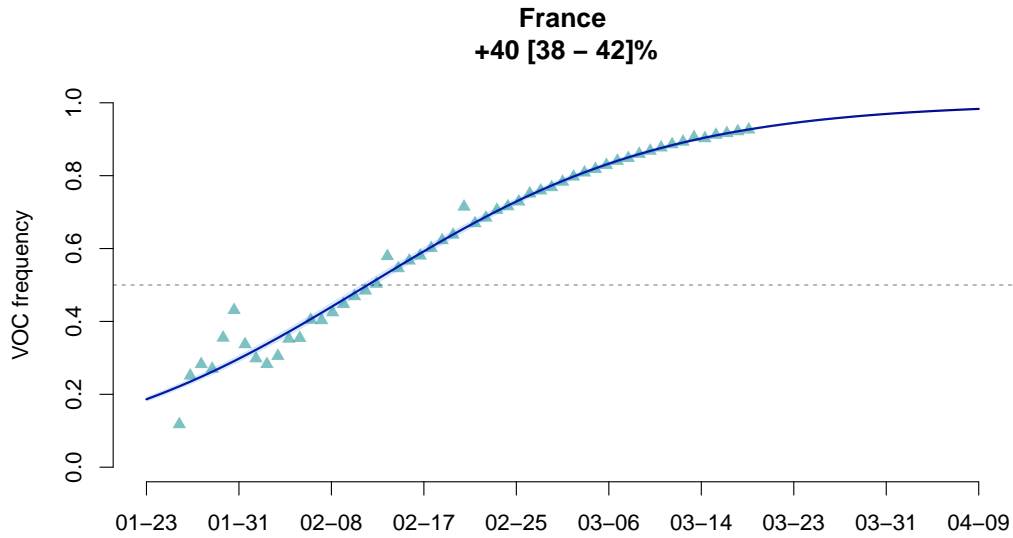


Figure S3: **Estimating the transmission advantage of the Alpha variant over the wild type strain.** The dots indicate the GLM-fitted values values and the line is the output of the logistic growth model estimation. The top figures indicate the estimated transmission advantage of the Alpha variant (with respect to the wild type reproduction number) and its 95%-confidence interval. The x-axis shows the date (month-day format).

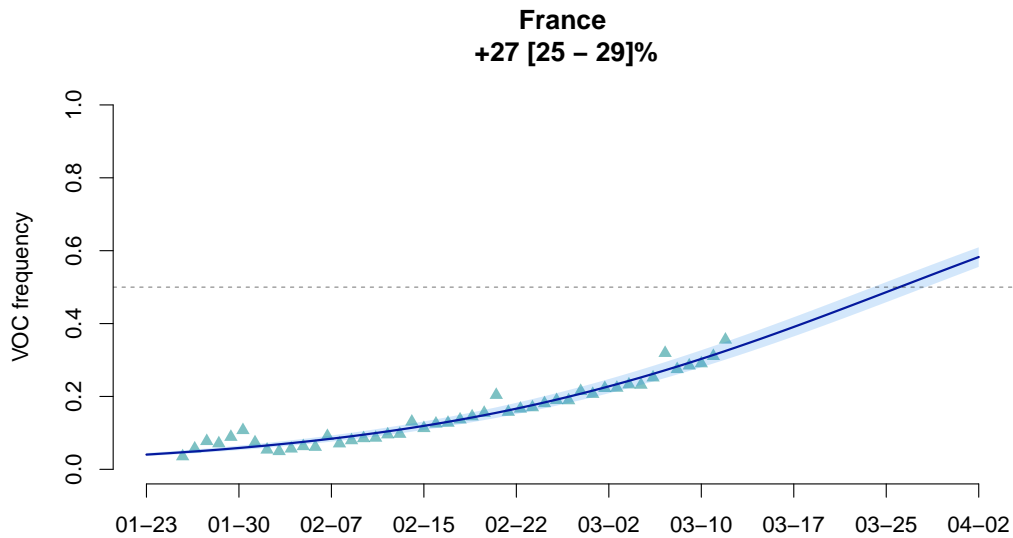


Figure S4: **Estimating the transmission advantage of the Beta or Gamma variants over the wild type strain.** See Figure S3 for details.

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