Characterization of vaccine-breakthrough infections of SARS-CoV-2 Delta and Alpha variants and within-host viral load dynamics in the community in France

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Abstract: We compare test results of SARS-CoV-2 positive patients, depending on their vaccine status, the presence of symptoms and whether they are infected by the Delta variant or not, using a large number of PCR tests done in the community in France from 14 June 2021 to 30 July 2021. In asymptomatic individuals, Ct values at the first positive test were higher in fully vaccinated individuals (> 2 weeks after final dose) than non fully vaccinated individuals (1.7 [1, 2.3], $p < 1e\text{-}6$). In *symptomatic* individuals however, Ct values at the time of symptoms were not significantly different in vaccinated compared to unvaccinated individuals ($p = 0.26$). This was true both for infections by Delta and non-Delta (essentially Alpha in France at the time) variants. These results imply that some infected vaccinated individuals, especially if symptomatic, may transmit the virus as much as unvaccinated individuals.

The SARS-CoV-2 variant of concern Delta, first detected in India, spread across the world in 2021, and in particular in Europe in late spring – early summer 2021, where it displaced the previously dominant Alpha variant. Delta was shown to be fitter than Alpha,[1–3] and may be associated with higher virulence[4,5] and lesser vaccine effectiveness[6,7] against symptomatic disease, especially after just one dose.

Delta has spread in countries with high vaccination levels, and breakthrough infections have been reported, with Ct values suggesting similar viral loads between vaccinated and unvaccinated infected individuals.[8–10] A longitudinal study has confirmed similar Ct values between Delta-infected vaccinated and unvaccinated patients in the first week after diagnosis or symptom onset, with later faster decline in vaccinated patients.[11] Comparisons of Ct values in infections with Delta compared to infections with previous variants require controlling for infection age when variants has different epidemiological dynamics. This is because viral load depends on infection age, and the distribution of infection ages depends on whether the number of cases is growing or shrinking.[12–16]

We studied the determinants of Ct values at the time of test and, for symptomatic individuals, as a function of the time since symptoms, in data from 292284 patients tested by a large private laboratory in the community in France, from 14 June 2021 to 30 July 2021 in three regions (Bretagne, Île-de-France, Provence-Alpes-Côte d'Azur). These data include information on the result of the PCR test, the associated Ct value, the patient's self-reported vaccine status (whether fully vaccinated since at least two weeks, or not), whether the patient has been symptomatic and the time since the onset of symptoms. Positive tests were screened for the L452R mutation, which characterizes the Delta variant (9343 positive tests with mutation information). In the case of multiple tests per individual, we kept the last negative test if there were no positive tests, and the first positive test otherwise.

Consistent with the French vaccination campaign, vaccinated individuals are on average older than non-vaccinated patients in our dataset (12 years older). The proportion of vaccinated individuals in the dataset (24%) is lower than in the community (47.5% by 10 July 2021), reflecting the fact that the data are not surveillance-based.

Reasons for testing may vary between vaccinated and non-vaccinated individuals. This may especially be the case since France introduced a "sanitary passport," requiring a proof of either full vaccination or a negative test for specific events, which may artificially inflate the proportion of negative tests among non-vaccinated individuals. Conversely, vaccinated individuals may get tested only if they have good reasons to suspect an infection.

We compared the cycle threshold (Ct; targeted at gene RdRp) values of the PCR of positive tests depending on vaccine status, the presence of symptoms, and the infecting variant (Delta: presence of the L452R mutation), for the 8437 individuals for which all pieces of information are available. The Ct is the number of PCR cycles needed to detect a target; it is negatively correlated with viral load. We find that the presence of symptoms is associated with significantly lower Ct values (-2.7 Ct [-3, -2.5]; adjusted $p < 1e\text{-}6$). An infection with the Delta variant is also associated with lower Ct values in these data (-6.7 Ct [-7.1, -6.3]; adjusted $p < 1e\text{-}6$)); note that age of infection is not controlled for here, but will be later on. Comparing vaccinated and non-vaccinated individuals, we find that vaccinated individuals have significantly higher Ct values for both Delta and non-Delta asymptomatic infections (1.7 [1, 2.3] Ct difference; adjusted $p < 1e\text{-}6$), but that the differences are not significant for symptomatic infections ($p = 0.8$). For non-Delta variants, this result may be due to too small a sample size (only $N = 18$ vaccinated symptomatic individuals infected with non-Delta).

Ct values also depend on the age of infection of tested individuals. It is therefore useful to control for age of infection, especially when comparing Ct values of variants with different epidemiological dynamics,[13,16] as was the case for the Delta (increasing numbers of infections) and Alpha (decreasing numbers of infections) in the early summer in France. To this end, we add time since symptoms onset as a continous variable in the linear model. We find that the Delta variant has Ct at day of symptoms -3.32 [-4.38, -2.25] lower than non-Delta (Alpha) ($p < 1e\text{-}6$, $N = 3439$). The slope of Ct as function of time is 0.6 [0.54, 0.66] per day for Delta and 0.92 [0.73, 1.1] for non-Delta variants (p < 1e-6). Vaccine status does not significantly alter the outcomes, whether regarding the Ct at symptom onset ($p = 0.256$) or the slope of Ct as function of time since symptoms ($p = 0.947$) and was therefore not included in the final model.

Limitations of our study stem from the way the data were collected: this is a community-based study. Reasons for seeking a PCR test are unknown and may vary among individuals and across time. Symptom and vaccine information are self-reported. Yet our dataset is unique for France, because variant information and vaccine status data have not been linked yet in public datasets, and Ct values are not reported at the national level (only test results are). Our results are in line with a retrospective cohort study which found lower Ct values with Delta and longer duration of infection with low Ct.[5] Regarding vaccine-breakthroughs, our results confirm studies finding similar Ct values among fully vaccinated individuals and those who were not, with the majority of infections being due to Delta.[8,9] Another limitation of our dataset is the lack of longitudinal data (in Figure 2, each point corresponds to a single patient). A recent study in Singapour found similar Ct values among vaccinated and unvaccinated individuals infected by Delta, at the time of diagnosis or of sympton onset.[11] After a week however, Ct values increased faster (i.e. viral load declined faster) among vaccinated individuals than unvaccinated individuals, even after excluding asymptomatic individuals (personal communication).[11] With transmission occuring early in infection, this delayed differential decrease is expected not to have much of an impact on relative transmissibility.

Ct values are linked to viral load, and viral load has been shown to be positively associated with probability of transmission in household contacts – but there is also high inter-individual variation, and transmission from individuals with high Ct values is possible.[17,18] In spite of these limitations, our confirmatory results indicate that epidemic control may require similar measures for symptomatic PCR-positive vaccinated individuals as non-vaccinated infected individuals.

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Figures

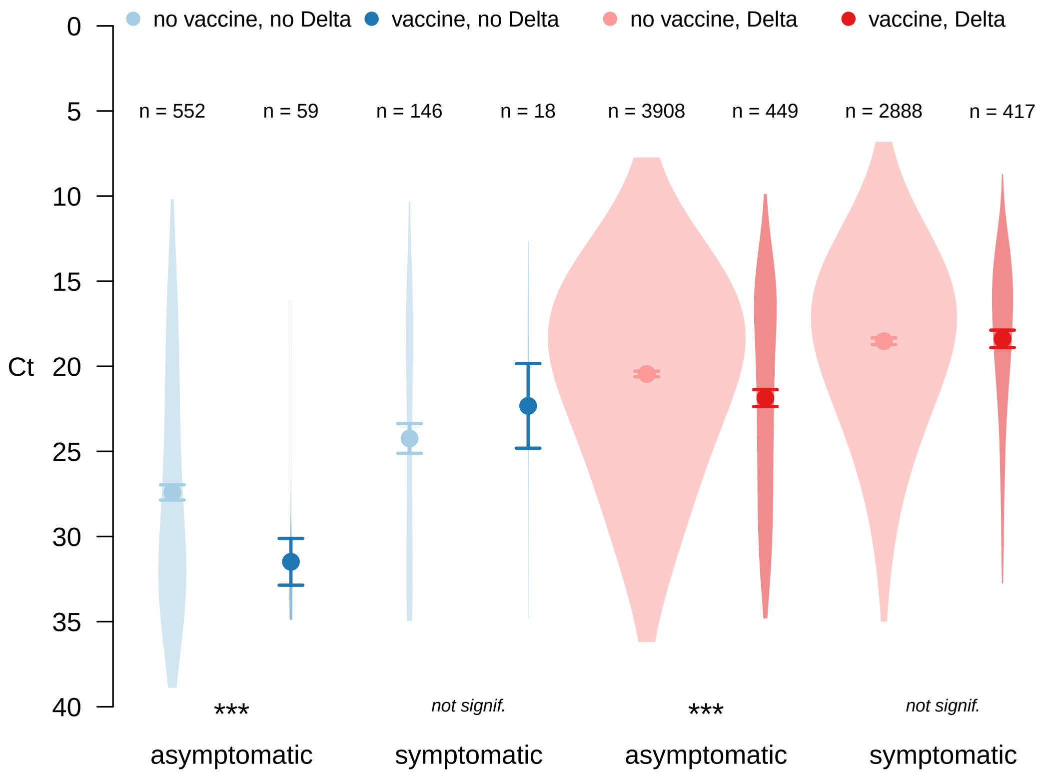

Figure 1: Distributions of Ct values, according to vaccine status (light: unvaccinated, dark: vaccinated), infecting variant (blue: non-Delta, red: Delta) and whether the individual was symptomatic (left: asymptomatic at least until the test, right: symptomatic). The widths of the violin plots reflect the number of tests; points and arrows represent predicted values and confidence intervals. "***" means that the corresponding comparison of unvaccinated and vaccinated individuals is statistically significant with $p < 0.001$.

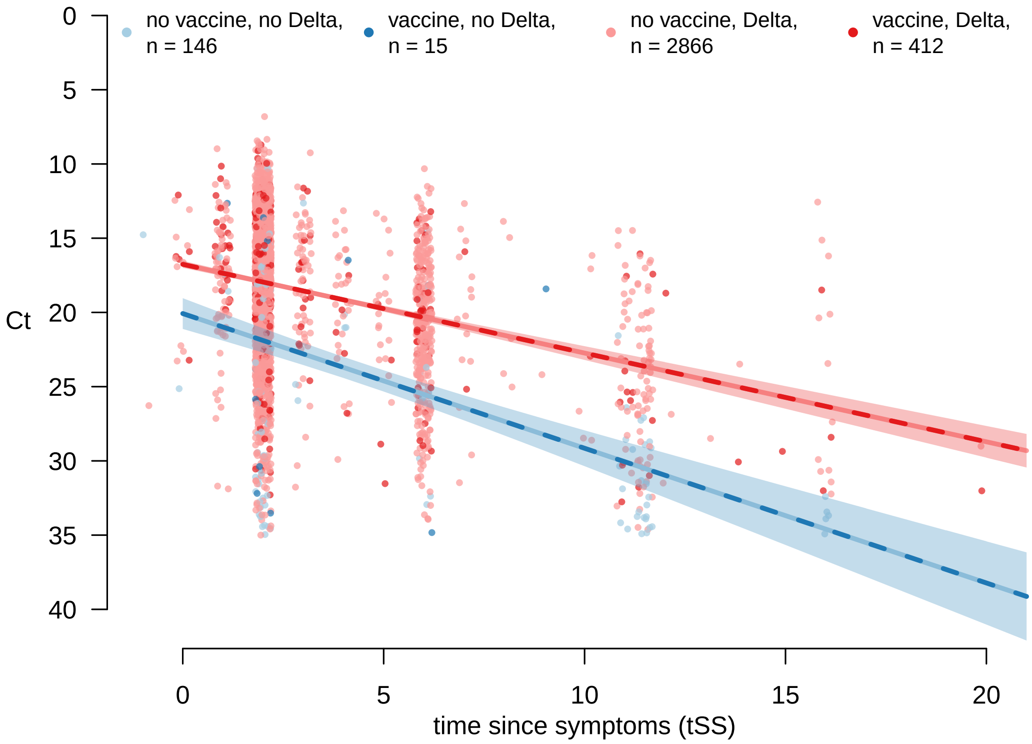

Figure 2: Regression of Ct value against time since symptoms, for symptomatic individuals, depending on vaccine status and infecting variant. The lines are the predicted values, the shaded areas the confidence intervals. The vaccination effect was not significant and therefore removed from the final model.

Appendix

Variables

name	type	description
`sympf`	factor (0, 1)	Whether the individual is fully vaccinated (1) or not (0)
`deltaf`	factor (0, 1)	Whether the L452R is detected (1) or not (0)
`vacf`	factor (0, 1)	Whether the individual is fully vaccinated (1) or not (0)
`Ct`	numeric	Ct value, RdRp gene
`tSS`	numeric	Time since symptom onset (days)

Model for Figure 1

```
mdlAov$call
```

```
## aov(formula = Ct ~ vacf * sympf * deltaf, data = tmp)
```

```
summary(mdlAov)
```

```
##                      Df Sum Sq Mean Sq  F value   Pr(>F)
## vacf                  1    351     351   12.108 0.000505 ***
## sympf                 1  15200   15200  524.896  < 2e-16 ***
## deltaf                1  32358   32358 1117.379  < 2e-16 ***
## vacf:sympf            1    775     775   26.766 2.35e-07 ***
## vacf:deltaf           1    144     144    4.970 0.025819 *
## sympf:deltaf          1    359     359   12.412 0.000429 ***
## vacf:sympf:deltaf     1    227     227    7.837 0.005130 **
## Residuals          8429 244096      29
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
thsd
```

```
##   Tukey multiple comparisons of means
##     95% family-wise confidence level
##
## Fit: aov(formula = Ct ~ vacf * sympf * deltaf, data = tmp)
##
## $vacf
##          diff       lwr      upr     p adj
## 1-0 0.6470032 0.2825148 1.011492 0.0005046
##
## $sympf
##          diff       lwr       upr p adj
## 1-0 -2.726566 -2.960009 -2.493124     0
##
```

```
## $deltaf
##         diff       lwr       upr p adj
## 1-0 -6.72394 -7.121566 -6.326314     0
##
## $`vacf:sympf`
##                diff        lwr        upr     p adj
## 1:0-0:0  1.6816459  1.0341760  2.3291159 0.0000000
## 0:1-0:0 -2.5080529 -2.8335307 -2.1825750 0.0000000
## 1:1-0:0 -2.7595748 -3.4541112 -2.0650384 0.0000000
## 0:1-1:0 -4.1896988 -4.8526381 -3.5267595 0.0000000
## 1:1-1:0 -4.4412207 -5.3445110 -3.5379303 0.0000000
## 1:1-0:1 -0.2515219 -0.9605014  0.4574576 0.7986775
##
## $`vacf:deltaf`
##                diff         lwr       upr     p adj
## 1:0-0:0  2.0758433   0.4153934  3.736293 0.0072293
## 0:1-0:0 -6.5769166  -7.1265213 -6.027312 0.0000000
## 1:1-0:0 -5.9746925  -6.6780558 -5.271329 0.0000000
## 0:1-1:0 -8.6527600 -10.2374675 -7.068052 0.0000000
## 1:1-1:0 -8.0505358  -9.6949058 -6.406166 0.0000000
## 1:1-0:1  0.6022242   0.1033012  1.101147 0.0104180
##
## $`sympf:deltaf`
##               diff       lwr       upr p adj
## 1:0-0:0 -3.824406 -5.040470 -2.608343     0
## 0:1-0:0 -7.225312 -7.822622 -6.628002     0
## 1:1-0:0 -9.324285 -9.933266 -8.715303     0
## 0:1-1:0 -3.400906 -4.500778 -2.301033     0
## 1:1-1:0 -5.499879 -6.606133 -4.393624     0
## 1:1-0:1 -2.098973 -2.417982 -1.779963     0
##
## $`vacf:sympf:deltaf`
##                         diff         lwr         upr     p adj
## 1:0:0-0:0:0   4.0748024   1.8402263   6.30937863 0.0000009
## 0:1:0-0:0:0  -3.1720965  -4.6903764  -1.65381653 0.0000000
## 1:1:0-0:0:0  -5.0857054  -8.9932302  -1.17818060 0.0020482
## 0:0:1-0:0:0  -6.9645855  -7.7063452  -6.22282583 0.0000000
## 1:0:1-0:0:0  -5.5406910  -6.5774897  -4.50389237 0.0000000
## 0:1:1-0:0:0  -8.8873726  -9.6453033  -8.12944188 0.0000000
## 1:1:1-0:0:0  -9.0238193 -10.0823280  -7.96531060 0.0000000
## 0:1:0-1:0:0  -7.2468989  -9.7636751  -4.73012268 0.0000000
## 1:1:0-1:0:0  -9.1605078 -13.5534270  -4.76758868 0.0000000
## 0:0:1-1:0:0 -11.0393880 -13.1792936  -8.89948235 0.0000000
## 1:0:1-1:0:0  -9.6154935 -11.8746836  -7.35630334 0.0000000
```

```
## 0:1:1-1:0:0 -12.9621750 -15.1077397 -10.81661041 0.0000000
## 1:1:1-1:0:0 -13.0986217 -15.3678571 -10.82938634 0.0000000
## 1:1:0-0:1:0  -1.9136089  -5.9890944   2.16187654 0.8466421
## 0:0:1-0:1:0  -3.7924891  -5.1676397  -2.41733844 0.0000000
## 1:0:1-0:1:0  -2.3685946  -3.9228736  -0.81431555 0.0001056
## 0:1:1-0:1:0  -5.7152761  -7.0992165  -4.33133582 0.0000000
## 1:1:1-0:1:0  -5.8517228  -7.4205671  -4.28287852 0.0000000
## 0:0:1-1:1:0  -1.8788802  -5.7330487   1.97528842 0.8194703
## 1:0:1-1:1:0  -0.4549857  -4.3766383   3.46666698 0.9999686
## 0:1:1-1:1:0  -3.8016672  -7.6589806   0.05564621 0.0567588
## 1:1:1-1:1:0  -3.9381139  -7.8655620  -0.01066581 0.0488069
## 1:0:1-0:0:1   1.4238945   0.6109881   2.23680092 0.0000031
## 0:1:1-0:0:1  -1.9227871  -2.3231923  -1.52238184 0.0000000
## 1:1:1-0:0:1  -2.0592338  -2.8996539  -1.21881362 0.0000000
## 0:1:1-1:0:1  -3.3466816  -4.1743701  -2.51899298 0.0000000
## 1:1:1-1:0:1  -3.4831282  -4.5926552  -2.37360130 0.0000000
## 1:1:1-0:1:1  -0.1364467  -0.9911733   0.71827990 0.9997296
```

Model for Figure 2

Full model

```
mdl$call
```

```
## lm(formula = Ct ~ vacf * deltaf * tSS, data = dat.nodupl)
```

```
car::Anova(mdl)
```

```
## Anova Table (Type II tests)
##
## Response: Ct
##                 Sum Sq   Df  F value    Pr(>F)
## vacf                27    1   1.2884  0.256427
## deltaf            3192    1 152.3081 < 2.2e-16 ***
## tSS               9487    1 452.6392 < 2.2e-16 ***
## vacf:deltaf          5    1   0.2289  0.632364
## vacf:tSS             0    1   0.0044  0.947141
## deltaf:tSS         211    1  10.0434  0.001542 **
## vacf:deltaf:tSS     44    1   2.1114  0.146299
## Residuals        71911 3431
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

Reduced model with significant effect only (used for the Figure)

```
mdl1$call
```

```
## lm(formula = Ct ~ deltaf + tSS + deltaf * tSS, data = dat.nodupl)
```

```
car::Anova(mdl1)
```

```
## Anova Table (Type II tests)
##
## Response: Ct
##            Sum Sq   Df F value    Pr(>F)
## deltaf       3231    1 154.156 < 2.2e-16 ***
## tSS          9512    1 453.905 < 2.2e-16 ***
## deltaf:tSS    228    1  10.872 0.0009863 ***
## Residuals   71987 3435
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```