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# 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],  $p < 1e-6$ ). 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 suggest that some infected vaccinated individuals, especially if symptomatic, may transmit the virus as much as unvaccinated individuals.

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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,<sup>1–3</sup> and may be associated with higher virulence<sup>4–6</sup> and lesser vaccine effectiveness<sup>6,7</sup> 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

18 individuals.<sup>8–10</sup> A longitudinal study has confirmed similar Ct values between Delta-infected vaccinated  
19 and unvaccinated patients in the first week after diagnosis or symptom onset, with later faster decline  
20 in vaccinated patients.<sup>11</sup> Comparisons of Ct values in infections with Delta compared to infections  
21 with previous variants require controlling for infection age when variants has different epidemiological  
22 dynamics. This is because viral load depends on infection age, and the distribution of infection ages  
23 depends on whether the number of cases is growing or shrinking.<sup>12–16</sup>

24 We studied the determinants of Ct values at the time of test and, for symptomatic individuals, as a  
25 function of the time since symptoms, in data from 292284 patients tested by a large private laboratory  
26 in the community in France, from 14 June 2021 to 30 July 2021 in three regions (Bretagne, Île-de-  
27 France, Provence-Alpes-Côte d’Azur). These data include information on the result of the PCR test,  
28 the associated Ct value, the patient’s self-reported vaccine status (whether fully vaccinated since at  
29 least two weeks, or not), whether the patient has been symptomatic and the time since the onset of  
30 symptoms. Positive tests were screened for the L452R mutation, which characterizes the Delta variant  
31 (9343 positive tests with mutation information). In the case of multiple tests per individual, we kept  
32 the last negative test if there were no positive tests, and the first positive test otherwise.

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

37 Reasons for testing may vary between vaccinated and non-vaccinated individuals. This may especially  
38 be the case since France introduced a “sanitary passport,” requiring a proof of either full vaccination  
39 or a negative test for specific events, which may artificially inflate the proportion of negative tests  
40 among non-vaccinated individuals. Conversely, vaccinated individuals may get tested only if they have  
41 good reasons to suspect an infection; these reasons may also vary if symptoms differ depending on the  
42 infecting variant.

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

56 Ct values also depend on the age of infection of tested individuals. It is therefore useful to control  
57 for age of infection, especially when comparing Ct values of variants with different epidemiological  
58 dynamics,<sup>13,16</sup> as was the case for the Delta (increasing numbers of infections) and Alpha (decreasing  
59 numbers of infections) in the early summer in France. To this end, we add time since symptoms onset

as a continuous 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) ( $p < 1e-6$ ,  $N = 3439$ ). 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 positive/negative 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.<sup>5</sup> 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.<sup>8,9</sup>

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 Singapore found similar Ct values among vaccinated and unvaccinated individuals infected by Delta, at the time of diagnosis or of symptom onset.<sup>11</sup> 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).<sup>11</sup> With transmission occurring 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.<sup>17,18</sup> 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, and that it is important to not to stop testing vaccinated individuals.

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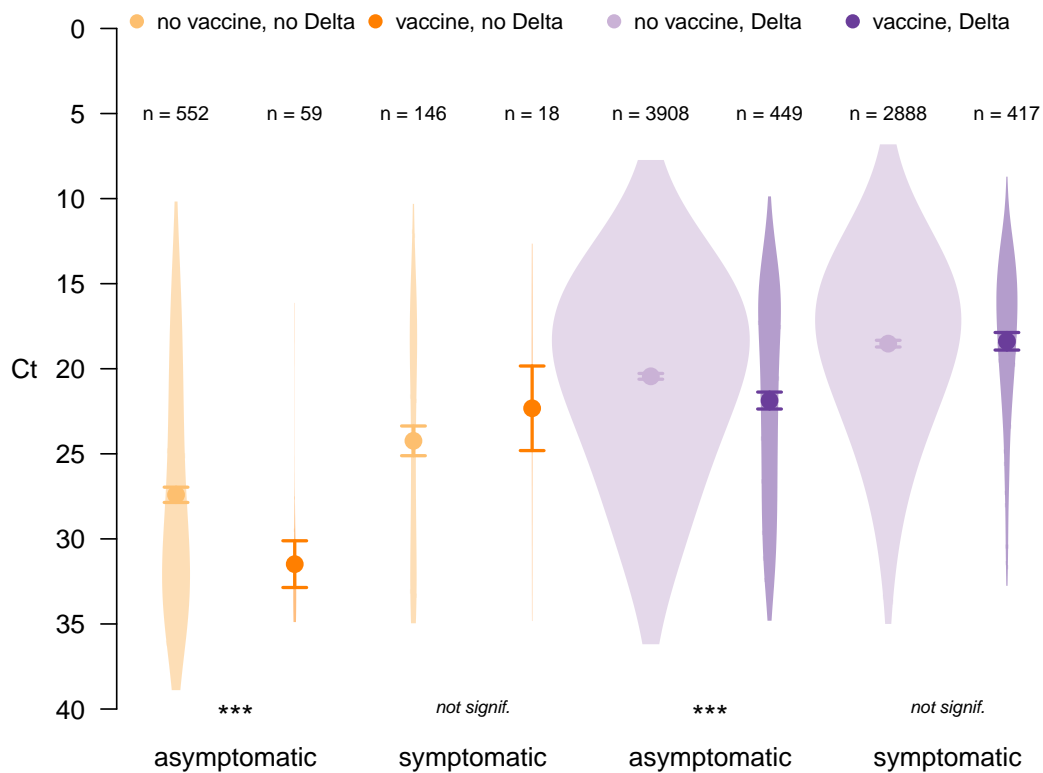
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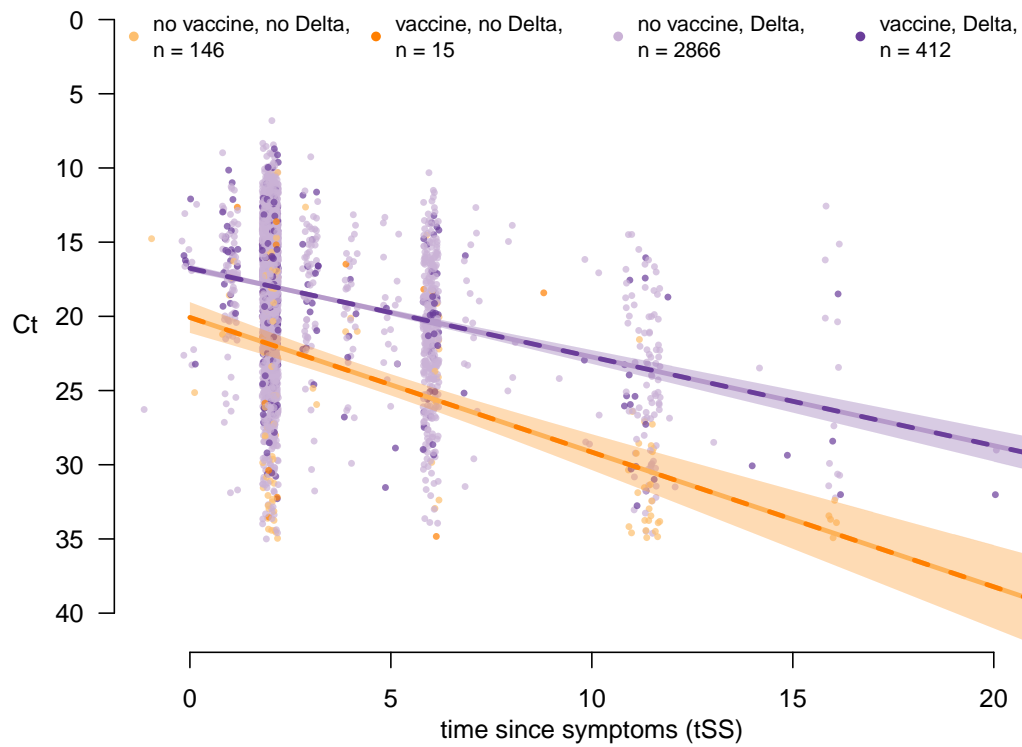
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## 88 Figures



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



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



## 99 Appendix

### 100 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)                           |

### 101 Model for Figure 1

```

102 mdlAov$call
102 ## aov(formula = Ct ~ vacf * sympf * deltax, data = tmp)
102 summary(mdlAov)

103 ##              Df Sum Sq Mean Sq  F value    Pr(>F)
104 ## vacf          1    351      351    12.108 0.000505 ***
105 ## sympf         1  15200   15200   524.896 < 2e-16 ***
106 ## deltax        1  32358   32358  1117.379 < 2e-16 ***
107 ## vacf:sympf    1    775     775    26.766 2.35e-07 ***
108 ## vacf:deltax   1    144     144     4.970 0.025819 *
109 ## sympf:deltax  1    359     359    12.412 0.000429 ***
110 ## vacf:sympf:deltax 1    227     227     7.837 0.005130 **
111 ## Residuals    8429 244096      29
112 ## ---
113 ## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

113 thsd

114 ## Tukey multiple comparisons of means
115 ## 95% family-wise confidence level
116 ##
117 ## Fit: aov(formula = Ct ~ vacf * sympf * deltax, data = tmp)
118 ##
119 ## $vacf
120 ##          diff          lwr          upr      p adj
121 ## 1-0 0.6470032 0.2825148 1.011492 0.0005046
122 ##
123 ## $sympf
124 ##          diff          lwr          upr p adj
125 ## 1-0 -2.726566 -2.960009 -2.493124 0
126 ##

```

```

127 ## $deltaf
128 ##          diff          lwr          upr p adj
129 ## 1-0 -6.72394 -7.121566 -6.326314      0
130 ##
131 ## $`vacf:sympf`
132 ##          diff          lwr          upr      p adj
133 ## 1:0-0:0  1.6816459  1.0341760  2.3291159 0.0000000
134 ## 0:1-0:0 -2.5080529 -2.8335307 -2.1825750 0.0000000
135 ## 1:1-0:0 -2.7595748 -3.4541112 -2.0650384 0.0000000
136 ## 0:1-1:0 -4.1896988 -4.8526381 -3.5267595 0.0000000
137 ## 1:1-1:0 -4.4412207 -5.3445110 -3.5379303 0.0000000
138 ## 1:1-0:1 -0.2515219 -0.9605014  0.4574576 0.7986775
139 ##
140 ## $`vacf:deltaf`
141 ##          diff          lwr          upr      p adj
142 ## 1:0-0:0  2.0758433  0.4153934  3.736293 0.0072293
143 ## 0:1-0:0 -6.5769166 -7.1265213 -6.027312 0.0000000
144 ## 1:1-0:0 -5.9746925 -6.6780558 -5.271329 0.0000000
145 ## 0:1-1:0 -8.6527600 -10.2374675 -7.068052 0.0000000
146 ## 1:1-1:0 -8.0505358 -9.6949058 -6.406166 0.0000000
147 ## 1:1-0:1  0.6022242  0.1033012  1.101147 0.0104180
148 ##
149 ## $`sympf:deltaf`
150 ##          diff          lwr          upr p adj
151 ## 1:0-0:0 -3.824406 -5.040470 -2.608343      0
152 ## 0:1-0:0 -7.225312 -7.822622 -6.628002      0
153 ## 1:1-0:0 -9.324285 -9.933266 -8.715303      0
154 ## 0:1-1:0 -3.400906 -4.500778 -2.301033      0
155 ## 1:1-1:0 -5.499879 -6.606133 -4.393624      0
156 ## 1:1-0:1 -2.098973 -2.417982 -1.779963      0
157 ##
158 ## $`vacf:sympf:deltaf`
159 ##          diff          lwr          upr      p adj
160 ## 1:0:0-0:0:0  4.0748024  1.8402263  6.30937863 0.0000009
161 ## 0:1:0-0:0:0 -3.1720965 -4.6903764 -1.65381653 0.0000000
162 ## 1:1:0-0:0:0 -5.0857054 -8.9932302 -1.17818060 0.0020482
163 ## 0:0:1-0:0:0 -6.9645855 -7.7063452 -6.22282583 0.0000000
164 ## 1:0:1-0:0:0 -5.5406910 -6.5774897 -4.50389237 0.0000000
165 ## 0:1:1-0:0:0 -8.8873726 -9.6453033 -8.12944188 0.0000000
166 ## 1:1:1-0:0:0 -9.0238193 -10.0823280 -7.96531060 0.0000000
167 ## 0:1:0-1:0:0 -7.2468989 -9.7636751 -4.73012268 0.0000000
168 ## 1:1:0-1:0:0 -9.1605078 -13.5534270 -4.76758868 0.0000000
169 ## 0:0:1-1:0:0 -11.0393880 -13.1792936 -8.89948235 0.0000000
170 ## 1:0:1-1:0:0 -9.6154935 -11.8746836 -7.35630334 0.0000000

```

|     |    |             |             |             |              |           |
|-----|----|-------------|-------------|-------------|--------------|-----------|
| 171 | ## | 0:1:1-1:0:0 | -12.9621750 | -15.1077397 | -10.81661041 | 0.0000000 |
| 172 | ## | 1:1:1-1:0:0 | -13.0986217 | -15.3678571 | -10.82938634 | 0.0000000 |
| 173 | ## | 1:1:0-0:1:0 | -1.9136089  | -5.9890944  | 2.16187654   | 0.8466421 |
| 174 | ## | 0:0:1-0:1:0 | -3.7924891  | -5.1676397  | -2.41733844  | 0.0000000 |
| 175 | ## | 1:0:1-0:1:0 | -2.3685946  | -3.9228736  | -0.81431555  | 0.0001056 |
| 176 | ## | 0:1:1-0:1:0 | -5.7152761  | -7.0992165  | -4.33133582  | 0.0000000 |
| 177 | ## | 1:1:1-0:1:0 | -5.8517228  | -7.4205671  | -4.28287852  | 0.0000000 |
| 178 | ## | 0:0:1-1:1:0 | -1.8788802  | -5.7330487  | 1.97528842   | 0.8194703 |
| 179 | ## | 1:0:1-1:1:0 | -0.4549857  | -4.3766383  | 3.46666698   | 0.9999686 |
| 180 | ## | 0:1:1-1:1:0 | -3.8016672  | -7.6589806  | 0.05564621   | 0.0567588 |
| 181 | ## | 1:1:1-1:1:0 | -3.9381139  | -7.8655620  | -0.01066581  | 0.0488069 |
| 182 | ## | 1:0:1-0:0:1 | 1.4238945   | 0.6109881   | 2.23680092   | 0.0000031 |
| 183 | ## | 0:1:1-0:0:1 | -1.9227871  | -2.3231923  | -1.52238184  | 0.0000000 |
| 184 | ## | 1:1:1-0:0:1 | -2.0592338  | -2.8996539  | -1.21881362  | 0.0000000 |
| 185 | ## | 0:1:1-1:0:1 | -3.3466816  | -4.1743701  | -2.51899298  | 0.0000000 |
| 186 | ## | 1:1:1-1:0:1 | -3.4831282  | -4.5926552  | -2.37360130  | 0.0000000 |
| 187 | ## | 1:1:1-0:1:1 | -0.1364467  | -0.9911733  | 0.71827990   | 0.9997296 |

## 188 **Model for Figure 2**

### 189 **Full model**

```
mdl$call

190 ## lm(formula = Ct ~ vacf * deltaf * tSS, data = dat.nodupl)
    car::Anova(mdl)

191 ## Anova Table (Type II tests)
192 ##
193 ## Response: Ct
194 ##              Sum Sq   Df F value    Pr(>F)
195 ## vacf              27    1   1.2884  0.256427
196 ## deltaf           3192    1 152.3081 < 2.2e-16 ***
197 ## tSS              9487    1 452.6392 < 2.2e-16 ***
198 ## vacf:deltaf        5    1   0.2289  0.632364
199 ## vacf:tSS           0    1   0.0044  0.947141
200 ## deltaf:tSS         211    1  10.0434  0.001542 **
201 ## vacf:deltaf:tSS    44    1   2.1114  0.146299
202 ## Residuals       71911 3431
203 ## ---
204 ## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

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

```
mdl1$call

206 ## lm(formula = Ct ~ deltaf + tSS + deltaf * tSS, data = dat.nodupl)
    car::Anova(mdl1)

207 ## Anova Table (Type II tests)
208 ##
209 ## Response: Ct
210 ##              Sum Sq   Df F value    Pr(>F)
211 ## deltaf           3231    1 154.156 < 2.2e-16 ***
212 ## tSS              9512    1 453.905 < 2.2e-16 ***
213 ## deltaf:tSS        228    1  10.872 0.0009863 ***
214 ## Residuals       71987 3435
215 ## ---
216 ## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```