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François Blanquart, Clémence Abad, Joevin Ambroise, Mathieu Bernard, Gina Cosentino, et al.. Characterization of vaccine-breakthrough infections of SARS-CoV-2 Delta and Alpha variants and within-host viral load dynamics in the community in France. 2021. hal-03318483v2

HAL Id: hal-03318483

<https://hal.sorbonne-universite.fr/hal-03318483v2>

Preprint submitted on 15 Aug 2021

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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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2021-08-15

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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.

10

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^{4–6} 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

18 individuals.^{8–10} 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.¹¹ 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.^{12–16}

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,^{13,16} 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

60 as a continuous variable in the linear model. We find that the Delta variant has Ct at day of symptoms
61 -3.32 [-4.38, -2.25] lower than non-Delta (Alpha) ($p < 1e-6$, $N = 3439$). The slope of Ct as function of
62 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
63 status does not significantly alter the outcomes, whether regarding the Ct at symptom onset ($p = 0.256$)
64 or the slope of Ct as function of time since symptoms ($p = 0.947$) and was therefore not included in the
65 final model.

66 Limitations of our study stem from the way the data were collected: this is a community-based
67 study. Reasons for seeking a PCR test are unknown and may vary among individuals and across time.
68 Symptom and vaccine information are self-reported. Yet our dataset is unique for France, because
69 variant information and vaccine status data have not been linked yet in public datasets, and Ct values
70 are not reported at the national level (only positive/negative test results are). Our results are in line with
71 a retrospective cohort study which found lower Ct values with Delta and longer duration of infection
72 with low Ct.⁵ Regarding vaccine-breakthroughs, our results confirm studies finding similar Ct values
73 among fully vaccinated individuals and those who were not, with the majority of infections being due
74 to Delta.^{8,9}

75 Another limitation of our dataset is the lack of longitudinal data (in Figure 2, each point corresponds
76 to a single patient). A recent study in Singapore found similar Ct values among vaccinated and
77 unvaccinated individuals infected by Delta, at the time of diagnosis or of symptom onset.¹¹ After a week
78 however, Ct values increased faster (i.e. viral load declined faster) among vaccinated individuals than
79 unvaccinated individuals, even after excluding asymptomatic individuals (personal communication).¹¹
80 With transmission occurring early in infection, this delayed differential decrease is expected not to
81 have much of an impact on relative transmissibility.

82 Ct values are linked to viral load, and viral load has been shown to be positively associated with
83 probability of transmission in household contacts – but there is also high inter-individual variation,
84 and transmission from individuals with high Ct values is possible.^{17,18} In spite of these limitations, our
85 confirmatory results indicate that epidemic control may require similar measures for symptomatic
86 PCR-positive vaccinated individuals as non-vaccinated infected individuals, and that it is important to
87 not to stop testing vaccinated individuals.

Acknowledgements

We thank Mircea Sofonea for critical comments on a previous version of the manuscript.

FB was funded by a Momentum grant from the Centre National de la Recherche Scientifique. FD was funded by grant ANR-19-CE45-0009-01 from Agence Nationale de la Recherche.

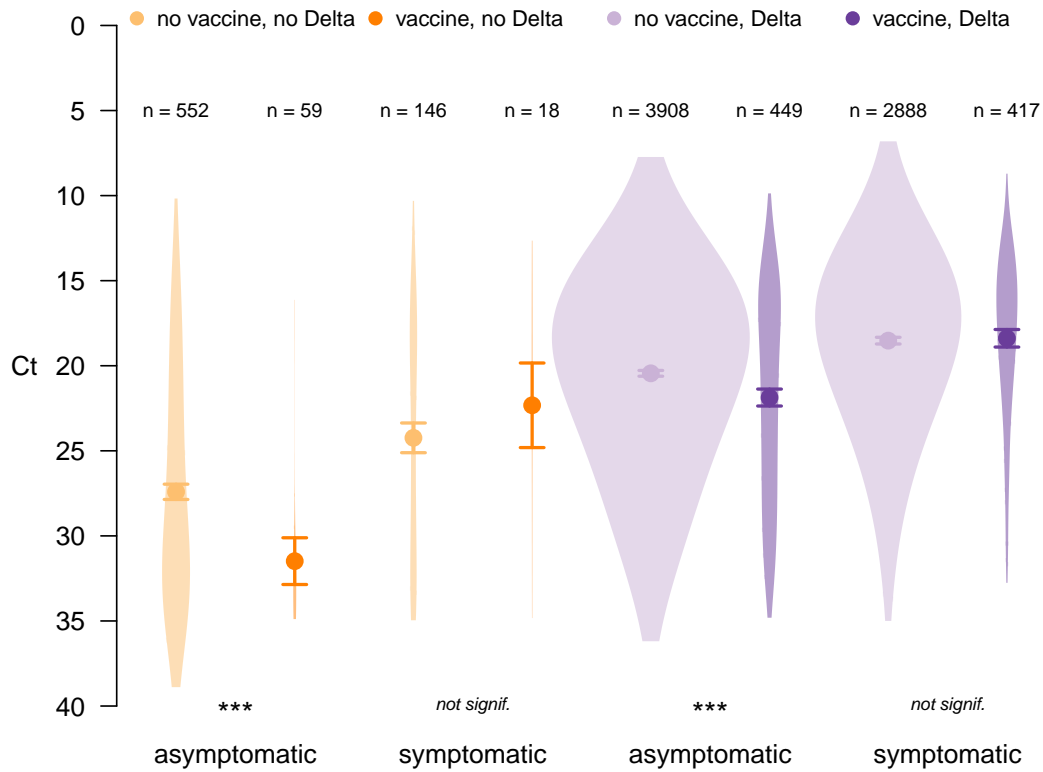
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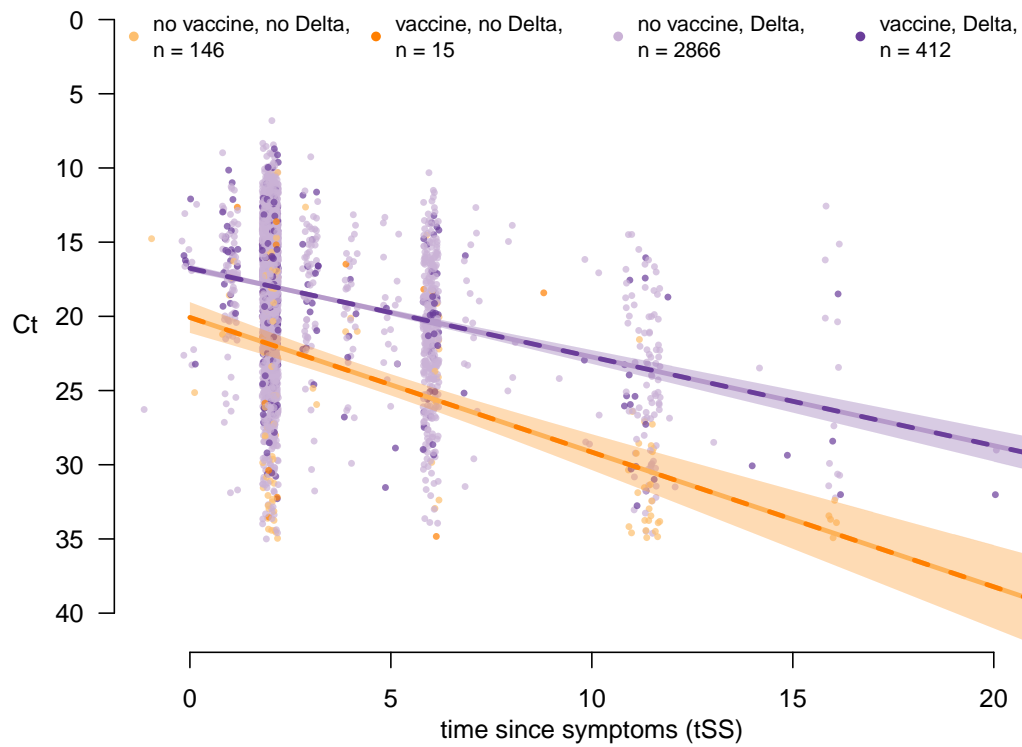
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88 Figures



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**

```

189 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)**

```

205 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

```