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1 **Virological and serological kinetics of SARS-CoV-2 Delta variant vaccine-**  
2 **breakthrough infections: a multi-center cohort study**

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24 **Keywords:** COVID-19; SARS-CoV-2; breakthrough infection; delta; variants of concern; vaccine

25 breakthrough; vaccination

## 26 **Objectives**

27 Highly effective vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have  
28 been developed but variants of concerns (VOCs) with mutations in the spike protein are worrisome,  
29 especially B.1.617.2 (Delta) which has rapidly spread across the world. We aim to study if vaccination  
30 alters virological and serological kinetics in breakthrough infections.

## 31 **Methods**

32 We conducted a multi-centre retrospective cohort study of patients in Singapore who had received a  
33 licensed mRNA vaccine and been admitted to hospital with B.1.617.2 SARS-CoV-2 infection. We  
34 compared the clinical features, virological and serological kinetics (anti-nucleocapsid, anti-spike and  
35 surrogate virus neutralization titres) between fully vaccinated and unvaccinated individuals.

## 36 **Results**

37 Of 218 individuals with B.1.617.2 infection, 84 had received a mRNA vaccine of which 71 were fully  
38 vaccinated, 130 were unvaccinated and 4 received a non-mRNA. Despite significantly older age in  
39 the vaccine breakthrough group, the odds of severe COVID-19 requiring oxygen supplementation  
40 was significantly lower following vaccination (adjusted odds ratio 0.07 95%CI: 0.015-0.335,  $p=0.001$ ).  
41 PCR cycle threshold (Ct) values were similar between both vaccinated and unvaccinated groups at  
42 diagnosis, but viral loads decreased faster in vaccinated individuals. Early, robust boosting of anti-  
43 spike protein antibodies was observed in vaccinated patients, however, these titers were  
44 significantly lower against B.1.617.2 as compared with the wildtype vaccine strain.

## 45 **Conclusion**

46 The mRNA vaccines are highly effective at preventing symptomatic and severe COVID-19 associated  
47 with B.1.617.2 infection. Vaccination is associated with faster decline in viral RNA load and a robust  
48 serological response. Vaccination remains a key strategy for control of COVID-19 pandemic.

49

## 50 **Background**

51 Availability of effective vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-  
52 2) within one year of the first report of coronavirus disease 2019 (COVID-19) is remarkable. Phase 3  
53 clinical trials of messenger RNA (mRNA) vaccines have demonstrated 92-95% efficacy in preventing  
54 symptomatic infection and severe disease [1-4] and intensive vaccination programs have reduced  
55 infection and mortality rates in multiple settings [5-7].

56 Emerging variants of concern (VOCs), such as B.1.1.7 (Alpha in the World Health Organization  
57 classification), B.1.351 (Beta), P.1 (Gamma), and B.1.617.2 (Delta) exhibit varied sequence changes  
58 and alteration of amino acid sequences of the spike protein. This has led to concerns of viral immune  
59 evasion and decreased vaccine effectiveness. Furthermore, these VOCs have been shown to be more  
60 transmissible [8-10], and B.1.1.7 and B.1.617.2 has been associated with increased disease severity  
61 and hospitalization [11, 12]. B.1.617.2 has rapidly spread outside India, becoming the most  
62 frequently sequenced lineage worldwide by end of June 2021 [13]. Case series of vaccine-  
63 breakthrough infections have reported an over-representation by these VOCs [14, 15].

64 Understanding vaccine effectiveness in the context of VOCs requires granular data: which vaccines  
65 were administered, at what time point prior to infection, number of doses, and particularly which  
66 VOC has caused the infection. Important VOC-specific vaccination outcomes include severity of  
67 infection and vaccine effects on transmission.

68 The COVID-19 vaccination program was initiated in Singapore on 30 December 2020, with free  
69 vaccinations provided to all Singapore residents in phases, beginning with the elderly and those in  
70 high-risk occupations such as healthcare workers. Vaccines used are mRNA vaccines,  
71 Pfizer/BioNTech BNT162b2 and Moderna mRNA-1273. As of 19 July 2021, 6,837,200 vaccine doses  
72 had been administered and ~2,792,430 individuals (47% of the total population) had completed the  
73 vaccination course [16]. In May 2021, B.1.617.2 became the dominant circulating variant based on  
74 local sequencing data.

75 In this multi-center cohort study, we characterize the clinical features, virological and serological  
76 kinetics of patients with vaccine-breakthrough PCR-confirmed B.1.617.2 infection and compared  
77 them with unvaccinated patients.

## 78 **Methods**

### 79 **Patient Recruitment**

80 Adults aged  $\geq 18$  years with COVID-19 confirmed by positive SARS-CoV-2 PCR and admitted to any of  
81 the five study sites from 1 April to 14 June 2021 were screened. Patients with B.1.617.2 infection  
82 (identification methods delineated below) were included in this analysis. Vaccine-breakthrough  
83 infection was defined as PCR-confirmed COVID-19 with symptom onset or first positive PCR  
84 (whichever was earlier)  $\geq 14$  days following a second dose of BNT162b2 or mRNA-1273 vaccine.  
85 Incomplete vaccination was defined as receipt of one dose of these vaccines  $\geq 14$  days prior to  
86 symptom onset or first positive PCR. Patients who received non-mRNA vaccines or developed  
87 infection within 14 days after the first dose were excluded from this analysis. B.1.617.2 vaccine-  
88 breakthrough infections were compared with a retrospective cohort of unvaccinated patients with  
89 B.1.617.2 infection admitted to one study site.

### 90 **Data Collection**

91 Clinical and laboratory data were collected from electronic medical records using a standardized  
92 data-collection form [17]. Laboratory data including cycle threshold (Ct) values from SARS-CoV-2 RT-  
93 PCR assays and serological results from Elecsys® (Roche, Basel, Switzerland) Anti-SARS-CoV-2  
94 chemiluminescent immunoassays [anti-nucleocapsid (anti-N) and anti-spike protein (anti-S)] and  
95 surrogate virologic neutralization test (sVNT) cPass™ (Genscript, NJ, USA) were recorded. cPass™  
96 detects total neutralizing antibodies targeting the viral spike protein receptor-binding domain [18].  
97 These tests were performed as part of routine clinical care.

### 98 **Additional Serologic testing**

99 Serum samples from a subset of vaccine-breakthrough patients who had separately consented for  
100 specimen collection were additionally tested with a newly developed multiplex-sVNT assay using the  
101 Luminex platform. Further details can be found in the supplementary information.

## 102 **Viral RNA sequencing and VOC determination**

103 SARS-CoV-2 PCR was performed using various commercially available assays in different clinical  
104 laboratories. As part of active genomic surveillance, whole genome sequencing (WGS) by National  
105 Public Health Laboratory is performed for all patients in Singapore with SARS-CoV-2 detected by RT-  
106 PCR with a Ct value less than 30. Pangolin COVID-19 Lineage Assigner and CoVsurver were used to  
107 assign lineage to each sequence. For individuals with PCR confirmed infection without available  
108 sequencing results, lineage was inferred based on epidemiological investigations by the Singapore  
109 Ministry of Health (MOH), and likely B.1.617.2 infections were included (i.e., clear epidemiologic link  
110 with patients with sequencing confirmed B.1.617.2 infection).

## 111 **Clinical Management**

112 All individuals with confirmed COVID-19 (including asymptomatic cases) in Singapore are admitted to  
113 hospital for inpatient evaluation and isolation. Individuals with pneumonia requiring supplemental  
114 oxygen are treated with intravenous remdesivir, while dexamethasone and other agents were  
115 reserved for progressive infections per national guidelines [19]. Disease severity was stratified into  
116 asymptomatic, mild (no pneumonia on chest radiography), moderate (presence of pneumonia on  
117 chest radiography), severe (requiring supplemental oxygen), or critical (requiring intensive care unit  
118 [ICU] admission or mechanical ventilation). Collection of clinical data was censored on discharge  
119 from hospital.

## 120 **Statistical Analysis**

121 For descriptive analysis, data were presented as median (interquartile range (IQR)) for continuous  
122 parameters and frequency (percentage) for categorical variables. Chi-square and Fisher's exact tests

123 were used to compared categorical variables, while for continuous variables, t-test was used for  
124 normal data and Mann-Whitney U test for non-normal data. For asymptomatic patients, the day of  
125 confirmatory COVID-19 diagnosis was denoted as day one of illness. For symptomatic patients, the  
126 day of symptom onset or the day of confirmatory COVID-19 diagnosis, whichever earlier, was  
127 denoted as day one of illness.

128 Previously reported risk factors for disease severity [20] were evaluated and included in a  
129 multivariate logistic regression model [21]. For serial Ct values, we fitted a generalized additive  
130 mixed model (GAMM) with a random intercept by patient. To investigate the effect of vaccination  
131 status on rate of increase of Ct value, we included fixed factors of vaccination status and day of  
132 illness with smoothing terms and interaction between these two fixed factors. We plotted Ct values  
133 with marginal effect of day of illness by vaccination status and 95% confidence intervals (CI) from the  
134 GAMM.

135 For analysis of cPass™ and anti-S titres we fitted a GAMM to serial titres with random intercept by  
136 patient in addition to fixed factor of day of illness with smoothing terms, separately for vaccine-  
137 breakthrough and unvaccinated patients infected with Delta variant. We plotted cPass™/anti-S titres  
138 with marginal effect of day of illness and 95%CI from GAMM for each group of vaccine-breakthrough  
139 and unvaccinated patients.

140 *P*-values less than 0.05 were considered statistically significant, and all tests were 2-tailed. Data  
141 analyses were performed using Stata Release 15 (StataCorp, College Station, TX) and R version 3.6.2  
142 (R Foundation for Statistical Computing, Vienna, Austria).

#### 143 **Ethical approval**

144 Written informed consent was obtained from study participants of the multi-centre study approved  
145 by National Healthcare Group Domain Specific Review Board (NHG-DSRB) (Study Reference

146 2012/00917). Informed consent for retrospective data collection at National Centre for Infectious  
147 Diseases (NCID) was waived (NHG-DSRB reference number 2020/01122).

## 148 **Results**

149 218 B.1.617.2 infections were identified across the five study sites (Supplementary Figure S1). Of  
150 these, 71 met the definition for vaccine-breakthrough. An additional 13 only received one dose  $\geq$ 14  
151 days prior to disease onset or received both doses but within 14 days of disease onset, while four  
152 had received a non-mRNA vaccine overseas. Majority of participants meeting study definition for  
153 vaccine-breakthrough had received two doses of BNT162b2 (n=66, 93%).

## 154 **Clinical Features**

155 In line with Singapore's national vaccination strategy wherein older adults were prioritized for  
156 vaccination, our vaccine-breakthrough cohort was of significantly older age; median age of 56 years  
157 (IQR:39-64) versus 39.5 (IQR:30-58) ( $p<0.001$ ) (Table 1). Other baseline demographics were similar.

158 Vaccine-breakthrough patients were significantly more likely to be asymptomatic (28.2% versus  
159 9.2%,  $p<0.001$ ); and if symptomatic, had fewer number of symptoms (Table 1). Unvaccinated  
160 individuals had worse levels of known biomarkers associated with increased COVID-19 severity  
161 including lymphocyte count, C-reactive protein [CRP], lactate dehydrogenase [LDH] and alanine  
162 transferase [ALT]. Correspondingly, a higher proportion of the unvaccinated cohort had pneumonia,  
163 required supplementary oxygen and ICU admission compared with the vaccinated cohort. A broader  
164 analysis comparing unvaccinated versus those who had received at least one dose of vaccine (i.e.  
165 both vaccine-breakthrough and incomplete vaccination) demonstrated similar findings  
166 (Supplementary Table T1).

167 Multivariate logistic regression analysis for development of severe COVID-19 (defined by  
168 supplementary oxygen requirement) demonstrated that vaccination was protective with an adjusted  
169 odds ratio (aOR) of 0.073 (95% confidence interval [CI]):0.016-0.343 ( $p=0.001$ ) (Table 2). Analysis



170 comparing unvaccinated versus those who had received at least one dose of vaccine demonstrated  
171 similar findings (Supplementary Table T2). Multivariate logistic regression analysis for development  
172 of moderately severe COVID-19 (defined by development of pneumonia) also demonstrated that  
173 vaccination was protective with aOR of 0.069 (95%CI:0.027-0.180) ( $p < 0.001$ ) (Supplementary Table  
174 T3).

### 175 **Virologic kinetics**

176 Serial Ct values of individuals were analyzed as a surrogate marker for the viral load. The initial  
177 median initial Ct value did not differ between unvaccinated and fully vaccinated patients  
178 (unvaccinated median Ct 18.8 (14.9-22.7), vaccinated 19.2 (15.2-22.2),  $p = 0.929$ ). However, fully  
179 vaccinated patients had a faster rate of increase in Ct value over time compared with unvaccinated  
180 individuals, suggesting faster viral load decline (coefficient estimates for interaction terms ranged  
181 from 9.12 (standard error 3.75) to 12.06 (standard error 3.03);  $p$ -value  $< 0.05$  for each interaction  
182 terms) (Figure 1).

### 183 **Serologic data**

184 69 fully vaccinated individuals and 45 unvaccinated had serologic data available on record. 66/66  
185 (100%) of vaccinated individuals had detectable S antibodies in week 1 of illness, while 7/45 (16%) of  
186 unvaccinated individuals did (Supplementary Figure S2). There was no difference in the proportion  
187 of individuals who seroconverted with the anti-N assay in week 1 (vaccinated 7/68 (10%) vs  
188 unvaccinated 11/107 (10%)) or week 2 (vaccinated 2/11 (18%), unvaccinated 4/20 (20%).

189 Analysis of sVNT with cPass indicated very high inhibition among vaccinated individuals in week 1 of  
190 illness (median 98.3% (IQR:91.0-99.4%)) which increased to 99.6% (IQR 99.3-99.9%) in week 2  
191 (Figure 2A, 2B). Among unvaccinated individuals, median inhibition was below the 20% threshold at  
192 both week 1 and week 2. Among the 37 vaccinated individuals with a serum sample available for

193 testing by the multiplex sVNT assay, titres were significantly higher against wildtype virus compared  
194 with B.1.617.2 and other VOCs (Figure 3). sVNT titres were lowest against B.1.617.2 and P.1 VOCs.

## 195 **Discussion**

196 In this study, we found that fully vaccinated patients had significantly lower odds of moderate or  
197 severe outcomes following infection by the SARS-CoV-2 VOC B.1.617.2. Vaccination was associated  
198 with lower peak measures of systemic inflammation, fewer symptoms, including more asymptomatic  
199 infection, and better clinical outcomes. Notably, in contrast to existing studies that showed lower  
200 viral load in vaccinated patients [22], initial viral load indicated by PCR Ct values was similar between  
201 vaccinated and unvaccinated patients with B.1.617.2. However, vaccinated patients appeared to  
202 clear viral load at a faster rate. Our serologic data suggest an early rapid rise in neutralizing and  
203 binding antibodies indicated by C-Pass and Roche anti-S antibodies, which may be evidence of  
204 memory immunity to COVID-19 vaccination on challenge with a breakthrough infection with  
205 B.1.617.2.

206 As part of active case finding and surveillance in Singapore, all patients with fever or respiratory  
207 symptoms, close contacts of confirmed cases, and newly arrived travelers are screened for COVID-19  
208 using PCR. Additionally, high-risk individuals in frontline occupations or congregate settings are  
209 tested as part of routine surveillance. All confirmed COVID-19 cases are reported to MOH and  
210 admitted to a hospital for initial evaluation. As such, our hospitalized cohort uniquely captures the  
211 entire spectrum of disease severity of COVID-19 infection and provides granular data even for mild  
212 and asymptomatic vaccine-breakthrough infections, giving us the opportunity to analyze virologic  
213 and serologic kinetics of these patients.

214 The finding of diminished severity with B.1.617.2 infection in vaccinated individuals is reassuring and  
215 corroborates emerging data from the United Kingdom which have found that mRNA vaccination  
216 remains protective against symptomatic and severe disease[12, 23]. An observational cohort study  
217 conducted in Scotland suggested that  $\geq 14$  days after the second dose, BNT162b2 vaccine offered

218 92% vaccine effectiveness against presumptive non-B.1.617.2 infection and 79% protection against  
219 presumptive B.1.617.2 [24]. Protection associated with the ChAdOx1 nCoV-19 vaccine was 73% and  
220 60% respectively. Although vaccine-breakthrough infections are increasingly reported, with the  
221 largest series to date in the United States reporting 10,262 breakthrough infections, a majority of  
222 these were mild (27% asymptomatic, 10% hospitalization, 2% mortality)[25]. Vaccine-breakthrough  
223 infections will continue to be observed, especially with genetic drift and selection pressures resulting  
224 in emergence of newer VOCs; however, it is likely that there will be a shift toward milder disease  
225 spectrum with more widespread implementation of vaccination programs.

226 To our knowledge, we provide the first data characterizing impact of vaccination on virologic kinetics  
227 by the B.1.617.2 variant. While initial Ct values were similar; the effect of vaccination with a more  
228 rapid decline in viral load (and hence shorter duration of viral shedding) has implications on  
229 transmissibility and infection control policy. A shorter duration of infectivity may allow a shorter  
230 duration of isolation for vaccinated individuals. Based on our data, it seems likely that vaccination  
231 reduces secondary transmission, though this needs to be further studied in larger community  
232 surveillance studies. Other studies found similar impact of vaccination on other variants. Pritchard  
233 and colleagues found that vaccinated individuals had higher Ct values compared with unvaccinated  
234 individuals in B.1.1.7 infections [7], while Levine-Tiefenbaum and colleagues similarly found a  
235 reduction in viral loads after BNT162b2 vaccine, though no data was provided on variant type [26].

236 There are several limitations to our study. Firstly, we only compared vaccine-breakthrough infections  
237 with unvaccinated COVID-19 patients. We did not study vaccinated individuals who had similar  
238 exposure risk but did not develop COVID-19 infection. We thus could not evaluate vaccine efficacy  
239 against asymptomatic infection. We also did not have detailed epidemiologic data to study the effect  
240 of vaccination on preventing secondary transmission.

241 Secondly, we could only obtain serologic tests after infection since patients were recruited after  
242 confirmation of infection. While active contact tracing and case finding in Singapore resulted in early

243 identification of most COVID-19 cases, the first available serologic result was at a median of 2 (IQR:1-  
244 3) days of illness and antibody levels are likely to already have been boosted by natural infection. We  
245 thus could not evaluate the underlying immunologic mechanisms behind vaccine-breakthrough  
246 infection, e.g., diminished neutralizing antibody level or impaired cellular immunity. Further study  
247 should compare similarly exposed vaccinated individuals who develop breakthrough infection with  
248 those who do not, to elucidate the underlying drivers of susceptibility, which may enlighten us on  
249 how to optimize protection (e.g., through enhanced/boosted dosing schedules).

250 Thirdly, PCR testing was not standardized in a centralized laboratory, and instead conducted at each  
251 centre using different validated commercial assays. Ct values are only a surrogate measure of viral  
252 load and shedding. We did not evaluate viability of shed virus via viral culture. In addition, we only  
253 evaluated participants with mRNA vaccination, and thus our findings are restricted to mRNA  
254 vaccines and not all COVID-19 vaccines.

## 255 **Conclusion**

256 mRNA vaccines against COVID-19 are protective against symptomatic infection and severe disease  
257 by the B.1.617.2 variant. Vaccinated individuals had a more rapid decline in viral load, which has  
258 implications on secondary transmission and public health policy. Rapid and widespread  
259 implementation of vaccination programs remains a key strategy for control of COVID-19 pandemic.  
260 Further studies should elucidate immunologic features driving vaccine-breakthrough infection to  
261 improve vaccine-induced protection.

262 **Conflict of Interest Disclosures**

263 BEY reports personal fees from Roche and Sanofi, outside the submitted work. All other authors  
264 declare no competing interests.

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274 management, analysis and interpretation of the data; preparation, review or approval of the  
275 manuscript; and decision to submit the manuscript for publication.

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	Unvaccinated n = 130	Vaccinated n = 71	p-value
Median age (IQR), years	39.5 (30-58)	56 (39-64)	<0.001
Male (%)	67 (51.5)	27 (38)	0.067
Median Charlson Comorbidity Index (IQR)	0 (0-1)	0 (0-0)	0.125
Diabetes mellitus (%)	28 (21.5)	5 (7.0)	0.008
Hypertension (%)	28 (21.5)	14 (19.7)	0.762
Hyperlipidaemia (%)	32 (24.6)	18 (25.4)	0.908
Median Ct value on diagnosis (IQR)*	18.8 (14.9-22.7)	19.2 (15.2-22.2)	0.929
Asymptomatic	12 (9.2)	20 (28.2)	<0.001
Symptom onset after Diagnosis (%)	11 (9.3)	11 (21.6)	0.030
Median day of illness symptoms start (IQR)	2 (2-3)	3 (2-3)	0.715
Median Ct values for Symptom Onset After (IQR)	21.87 (18.8-31.2)	19.2 (16.6-21.5)	0.279
Median Sum of Symptoms Reported (IQR)	2 (1-3)	1 (0-2)	<0.001
Fever (%)	96 (73.9)	29 (40.9)	<0.001
Cough (%)	79 (60.8)	27 (38)	0.002
Shortness of Breath (%)	17 (13.1)	1 (1.4)	0.004
Runny Nose (%)	31 (23.9)	27 (38)	0.034
Sore Throat (%)	43 (33.1)	18 (25.4)	0.255
Diarrhoea (%)	8 (6.2)	0	0.052
Median highest Neutrophil (IQR) × 10 <sup>9</sup> /L	4.50 (3.07-5.92)	4.33 (3.52-5.43)	0.117
Median lowest Lymphocyte (IQR) × 10 <sup>9</sup> /L	0.95 (0.65-1.50)	1.36 (1.02-1.87)	<0.001
Median highest C-Reactive Protein (IQR), mg/L	24.7 (6.9-84.8)	12.6 (6.5-22.5)	<0.001
Median highest Lactate Dehydrogenase (IQR), U/L	486 (365-672)	373 (314-421)	0.062
Median highest Alanine Transferase (IQR), U/L	35	19	<0.001

	(18-74)	(13-34)	
<b>Disease Outcome</b>			
Pneumonia (%)	69 (53.1)	9 (21.7)	<0.001
Supplementary O2 required (%)	27 (20.8)	2 (2.8)	<0.001
ICU admission required (%)	7 (5.4)	0	0.053
Median days of ICU admission required (IQR)	4 (3-9)	-	-
Intubation (%)	2 (1.5)	0	0.541
Median days of Intubation (IQR)	7 (3-11)	-	-
COVID-19 specific treatment (%)	39 (30)	5 (7)	<0.001
Mortality	2 (1.54)	0	0.541

289

290 Table 1: Baseline characteristics and disease outcome between unvaccinated and completed mRNA

291 vaccination COVID-19 B.1.617.2 infected patients

292

	Univariable model		Multivariable model	
	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Vaccinated	0.111 (0.025-0.480)	0.003	0.073 (0.016-0.343)	0.001
Age group				
<45 years old	1	-	1	-
45-64 years old	6.19 (1.90-20.2)	0.003	8.29 (2.29-30.0)	0.001
>64 years old	13 (3.90-42.9)	<0.001	13.5 (2.66-68.8)	0.002
Male	0.913 (0.414-2.01)	0.821	1.09 (0.418-2.85)	0.857
Diabetes	6.18 (2.59-14.7)	<0.001	2.24 (0.785-6.41)	0.132
Hypertension	4.8 (2.09-11.0)	<0.001	1.62 (0.509-5.18)	0.413
Presence of other comorbidities, if any	3.96 (1.66-9.44)	0.002	0.897 (0.262-3.07)	0.862

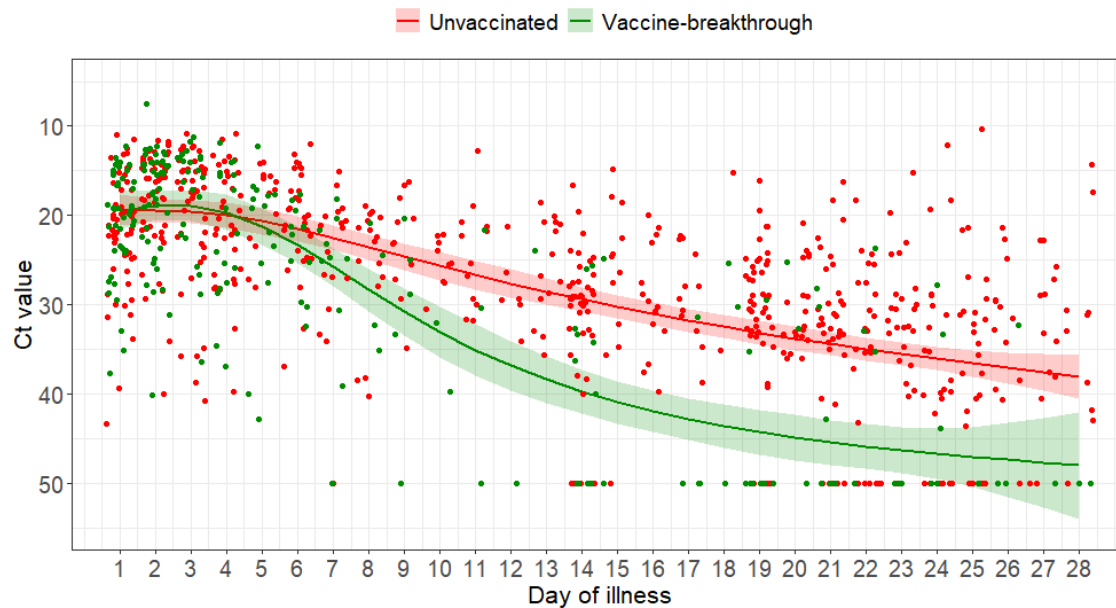
293

294 **Table 2:** Odds ratio of candidate risk factors for development of severe COVID-19 for completed  
 295 mRNA vaccination COVID-19 B.1.617.2 infected patients. CI, confidence interval; OR, odds ratio

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299 **Figure 1:** Scatterplot of Ct values and marginal effect of day of illness of COVID-19 B1.617.2 infected  
300 patients with 95% confidence intervals from generalized additive mixed model with interaction term  
301 between vaccination status and day of illness

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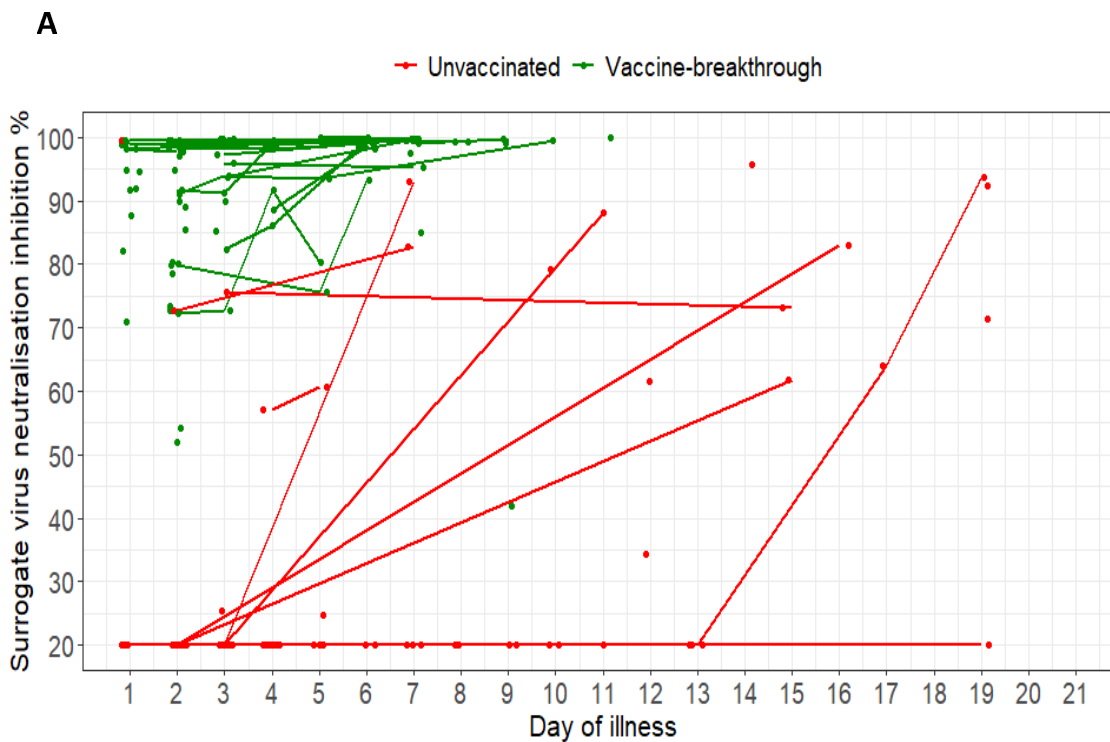
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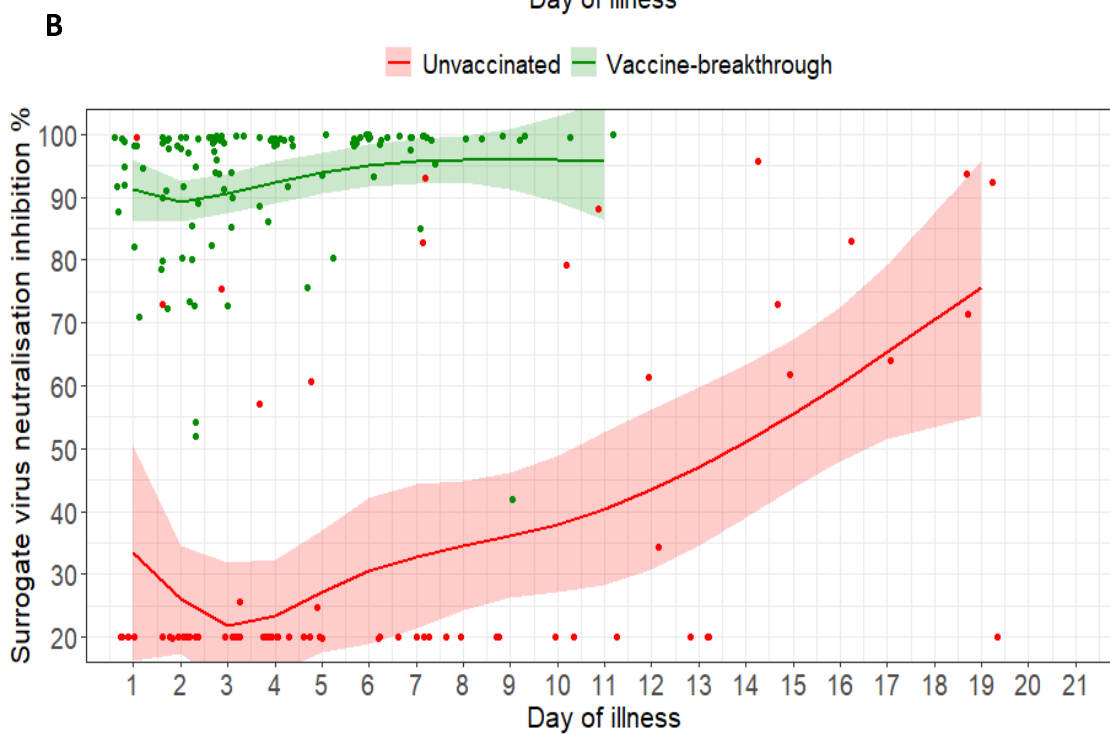
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310 **Figure 2:** (A) Spaghetti plot of surrogate virus neutralisation (sVNT) inhibition % as measured by

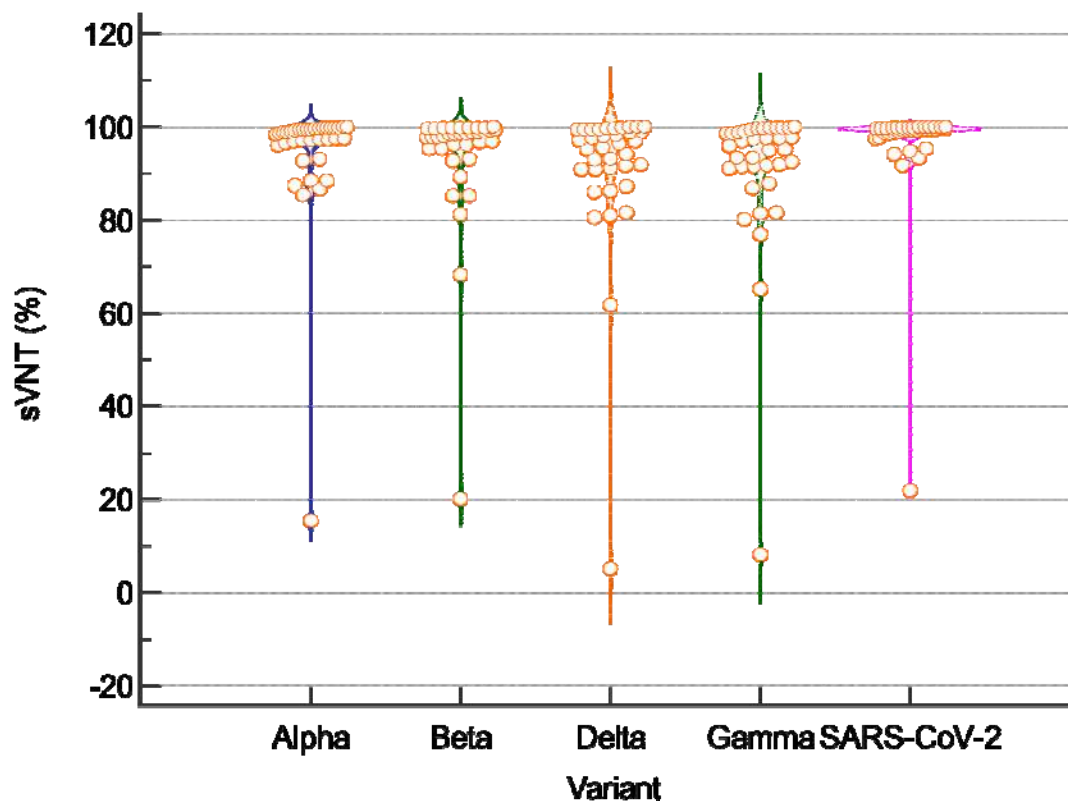
311 cPass; (B) Scatterplot of sVNT inhibition % and marginal effect of day of illness by vaccine-

312 breakthrough and unvaccinated groups of COVID-19 B.1.617.2 infected patients with 95% confidence

313 intervals from generalized additive mixed models. For both plots, n=127; vaccine-breakthrough = 67,  
314 unvaccinated = 60

315

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317

318 **Figure 3:** Violin plots of of surrogate virus neutralisation (sVNT) inhibition % against wildtype SARS-  
319 CoV-2 and the B.1.617.2 variant for 36 patients with vaccine-breakthrough infection (median day of  
320 sample collection from infection onset 6 days (inter-quartile range (IQR) 3-7). Titres against the four  
321 variants were significantly lower than against wildtype SARS-CoV-2 [median sVNT, B.1.1.7 98.5%  
322 (IQR: 96.3-99.5); B.1.351 98.2% (IQR: 95.3-99.5); B.1.617.2 96.0% (IQR: 90.9-99.3); P.1 95.5% (IQR:  
323 91.3-98.9); Wildtype 99.4% (IQR: 98.5-99.7), Kruskal-Wallis p-value = 0.00055, Post-hoc pairwise  
324 comparison (Conover) Wildtype versus each variant p<0.05]

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