

1 **Transmission of SARS-CoV-2 Delta variant among vaccinated**  
2 **healthcare workers, Vietnam**

3 Nguyen Van Vinh Chau<sup>1</sup>, Nghiem My Ngoc<sup>1</sup>, Lam Anh Nguyet<sup>2</sup>, Vo Minh Quang<sup>1</sup>,  
4 Nguyen Thi Han Ny<sup>2</sup>, Dao Bach Khoa<sup>1</sup>, Nguyen Thanh Phong<sup>1</sup>, Le Mau Toan<sup>1</sup>, Nguyen  
5 Thi Thu Hong<sup>2</sup>, Nguyen Thi Kim Tuyen<sup>2</sup>, Voong Vinh Phat<sup>2</sup>, Le Nguyen Truc Nhu<sup>2</sup>,  
6 Nguyen Huynh Thanh Truc<sup>1</sup>, Bui Thi Ton That<sup>1</sup>, Huynh Phuong Thao<sup>1</sup>, Tran Nguyen  
7 Phuong Thao<sup>1</sup>, Vo Trong Vuong<sup>1</sup>, Tran Thi Thanh Tam<sup>1</sup>, Ngo Tan Tai<sup>1</sup>, Ho The Bao<sup>1</sup>,  
8 Huynh Thi Kim Nhung<sup>1</sup>, Nguyen Thi Ngoc Minh<sup>1</sup>, Nguyen Thi My Tien<sup>1</sup>, Nguy Cam  
9 Huy<sup>1</sup>, Marc Choisy<sup>2,3</sup>, Dinh Nguyen Huy Man<sup>1</sup>, Dinh Thi Bich Ty<sup>1</sup>, Nguyen To Anh<sup>2</sup>, Le  
10 Thi Tam Uyen<sup>1</sup>, Tran Nguyen Hoang Tu<sup>1</sup>, Lam Minh Yen<sup>2</sup>, Nguyen Thanh Dung<sup>1</sup>, Le  
11 Manh Hung<sup>1</sup>, Nguyen Thanh Truong<sup>1</sup>, Tran Tan Thanh<sup>2</sup>, Guy Thwaites<sup>2,3</sup>, and Le Van  
12 Tan<sup>2</sup>, for the OUCRU COVID-19 research group\*

13 **Affiliations**

14 <sup>1</sup>Hospital for Tropical Diseases, Ho Chi Minh City, Vietnam

15 <sup>2</sup>Oxford University Clinical Research Unit, Ho Chi Minh City, Vietnam

16 <sup>3</sup>Centre for Tropical Medicine and Global Health, Nuffield Department of Medicine,  
17 University of Oxford, Oxford, UK

18 \*Members are listed in the Acknowledgements.

19 Correspondence: Nguyen Van Vinh Chau, [chaunvv@oucru.org](mailto:chaunvv@oucru.org), Le Van Tan,  
20 [tanlv@oucru.org](mailto:tanlv@oucru.org)

21 **Word count:** abstract: 250 words, full text 2354 words

22 **Key words:** Delta variant, Oxford-AstraZeneca, COVID-19, vaccine breakthrough,  
23 Vietnam

24 **ABSTRACT**

25 **Background:** Data on breakthrough SARS-CoV-2 Delta variant infections are limited.

26 **Methods:** We studied breakthrough infections among healthcare workers of a major  
27 infectious diseases hospital in Vietnam. We collected demographics, vaccination history  
28 and results of PCR diagnosis alongside clinical data. We measured SARS-CoV-2  
29 (neutralizing) antibodies at diagnosis, and at week 1, 2 and 3 after diagnosis. We  
30 sequenced the viruses using ARTIC protocol.

31 **Findings:** Between 11<sup>th</sup>–25<sup>th</sup> June 2021 (week 7–8 after dose 2), 69 healthcare workers  
32 were tested positive for SARS-CoV-2. 62 participated in the clinical study. 49 were  
33 (pre)symptomatic with one requiring oxygen supplementation. All recovered uneventfully.  
34 23 complete-genome sequences were obtained. They all belonged to the Delta variant, and  
35 were phylogenetically distinct from the contemporary Delta variant sequences obtained  
36 from community transmission cases, suggestive of ongoing transmission between the  
37 workers. Viral loads of breakthrough Delta variant infection cases were 251 times higher  
38 than those of cases infected with old strains detected between March-April 2020. Time  
39 from diagnosis to PCR negative was 8–33 days (median: 21). Neutralizing antibody levels  
40 after vaccination and at diagnosis of the cases were lower than those in the matched  
41 uninfected controls. There was no correlation between vaccine-induced neutralizing  
42 antibody levels and viral loads or the development of symptoms.

43 **Interpretation:** Breakthrough Delta variant infections are associated with high viral loads,  
44 prolonged PCR positivity, and low levels of vaccine-induced neutralizing antibodies,  
45 explaining the transmission between the vaccinated people. Physical distancing measures  
46 remain critical to reduce SARS-CoV-2 Delta variant transmission.

47 **Funding:** Wellcome (106680/B/14/Z and 204904/Z/16/Z).

Preprint not peer reviewed

## 48 **RESEARCH IN CONTEXT**

### 49 **Evidence before this study**

50 We conducted a literature search of PubMed Central for studies or reports of SARS-CoV-2  
51 breakthrough infections up to 1<sup>st</sup> August 2021. We used the terms “breakthrough Delta  
52 variant infection”, “Delta variant breakthrough infection” and “SARS-CoV-2  
53 breakthrough infections” without language restriction. We identified 14 relevant scientific  
54 papers including one published in medRxiv. Of these, only the medRxiv paper described 6  
55 cases of breakthrough Delta variant infections. Of the remaining 12, 10 described  
56 breakthrough infections associated with non-Delta variants of concerns (Alpha, Beta and  
57 Gama variants).

58 None of the above mentioned studies described the transmission between vaccinated  
59 people, while one study reported the transmission between vaccinated people and  
60 household members. Likewise, there was only one paper comparing the viral loads  
61 between fully vaccinated and partially vaccinated individuals with breakthrough Alpha  
62 variant infection and found no difference between the two group. And there was one paper  
63 comparing the viral load between vaccinated and unvaccinated people infected with the  
64 Alpha variant but found no difference in viral load between the two groups. Only one  
65 paper had follow-up data on PCR testing after infection and found low viral loads and  
66 short duration of viral shedding (2-7 days) in cases of breakthrough infections without  
67 information about the causal variant. Most recently, a study in Israel identified a  
68 correlation between neutralizing antibody titers after the second dose and at diagnosis and  
69 break through infection. The causal variant was the Alpha variant.

### 70 **Added value of this study**

71 We studied 62 breakthrough cases among healthcare workers of a major hospital for  
72 infectious diseases in Ho Chi Minh City (HCMC), Vietnam between 11<sup>th</sup>-25 June 2021.  
73 We captured the infected cases at a very early phase of the infection and carefully followed  
74 them up during hospitalization to assess the kinetic of viral loads and neutralizing  
75 antibodies, and the development of clinical symptoms. To dissect the epidemiological link  
76 and the transmission potential between the vaccinated healthcare workers, we conducted  
77 whole genome sequencing of SARS-CoV-2.  
78 49/62 case patients were (pre)symptomatic) and all recovered uneventfully. A total of 23  
79 complete genome sequences were obtained from the breakthrough cases. The obtained  
80 sequences were all belonged to the Delta variant, but distinct from contemporary  
81 sequences obtained from cases of community transmission in HCMC, suggesting that the  
82 ongoing transmission had occurred between vaccinated healthcare workers. Viral loads  
83 peaked at around 2-3 days before and after the development of clinical symptoms with  
84 prolonged PCR positivity of up to 33 days. Viral loads were 251 times higher than those in  
85 cases infected with old SARS-CoV-2 strains detected in Vietnam between March and  
86 April 2020. Vaccine-induced neutralizing antibodies after the second dose and at diagnosis  
87 were lower than those in the matched uninfected controls. There was no correlation  
88 between vaccine-induced neutralizing antibody levels and viral loads (i.e. infectivity) or  
89 the development of symptoms during the course of infection.

#### 90 **Implications of all the available evidence**

91 Our study provided strong evidence demonstrating for the first time the transmission  
92 between vaccine breakthrough cases infected with the Delta variant. High viral loads  
93 coupled with prolonged PCR positivity and poorly ventilated indoor setting without in-

94 office mask wearing might have facilitated the transmission between vaccinated healthcare  
95 workers. The absence of correlation between neutralizing antibody levels and peak viral  
96 loads suggested that vaccine might not lower the infectivity of breakthrough cases. Given  
97 the rapid spread of the Delta variant worldwide, physical distancing measures remain  
98 critical to reduce the transmission of SARS-CoV-2 Delta variant, event in countries where  
99 vaccination coverage is high.

## 100 INTRODUCTION

101 SARS-CoV-2 Delta variant is approximately 60% more transmissible than the Alpha  
102 (B.1.1.7) variant, and has rapidly spread worldwide<sup>1</sup>, posing a significant threat to global  
103 COVID-19 control. The Delta variant possesses mutations in the spike protein (including  
104 L452R and T478K) that makes the virus less susceptible to neutralizing antibodies  
105 generated by current vaccines or natural infection.<sup>2,3</sup> This has raised concern about vaccine  
106 escape potential.

107 Data on vaccine breakthrough infections, especially those caused by the Delta variant, are  
108 limited.<sup>4</sup> Likewise, it remains unknown regarding the transmission potential of vaccine  
109 breakthrough infection cases, especially those infected with the Delta variant. These data  
110 however are critical to informing the development and deployment of COVID-19 vaccine,  
111 and the implementation of infection control measures. Here, we investigate breakthrough  
112 SARS-CoV-2 Delta variant infections among double-vaccinated healthcare workers of a  
113 major infectious diseases hospital in Ho Chi Minh City (HCMC), Vietnam.

## 114 MATERIALS AND METHODS

### 115 Setting

116 The study was conducted at the Hospital for Tropical Diseases (HTD) in HCMC. HTD is a  
117 550-bed tertiary referral hospital for patients with infectious diseases in southern Vietnam.<sup>5</sup>  
118 The hospital has around 900 members of staff and 34 departments. All offices, except one,  
119 one are equipped with air conditioners that recirculate the air without mechanical  
120 ventilation (Supplementary Figure 1).

121 HTD staff members were amongst the first people in Vietnam to be offered the Oxford-  
122 AstraZeneca COVID-19 vaccine. The first doses were given on 8<sup>th</sup> March 2021; the second  
123 doses were given in the last two weeks of April 2021.<sup>6</sup>

#### 124 **Data collection**

125 We collected demographics, vaccination history and clinical data alongside the results of  
126 SARS-CoV-2 PCR diagnosis from the study participants. For SARS-CoV-2 antibody  
127 measurement, we obtained 2ml of EDTA plasma from each study participants at diagnosis  
128 and at week 1, 2 and 3 after admission.

#### 129 **Nasopharyngeal-throat swab collection, PCR testing and viral load conversion**

130 Nasopharyngeal swabs were collected and placed in 1mL of viral transport medium, and  
131 200uL was used for viral RNA extraction using the MagNApure 96 platform (Roche  
132 Diagnostics, Germany), according to the manufacturer's instructions. For SARS-CoV-2  
133 RNA detection, we used real-time RT-PCR assay with primers and probe targeted at the  
134 envelope protein-coding gene (TIB MOLBIOL)<sup>7</sup>. PCR Ct values were converted to RNA  
135 loads using an in-house established formula ( $y = -0.3092x + 12.553$ ,  $R^2 = 0.9963$ , where  $y$   
136 is viral load and  $x$  is Ct value) based on 10-fold dilution series of in-vitro transcribed  
137 RNA<sup>7,8</sup>.

#### 138 **Whole genome sequencing and sequence analysis**

139 Whole-genome sequences of SARS-CoV-2 were directly obtained from leftover RNA after  
140 PCR testing using ARTIC protocol and Illumina reagents on a MiSeq platform with the  
141 inclusion of a negative control in every sequencing run. The obtained reads from individual  
142 samples were mapped to a SARS-CoV-2 reference genome (GISAID sequence ID:  
143 EPI\_ISL\_1942165) to generate the consensus using Geneious software (Biomatter, New



144 Zealand). SARS-CoV-2 variant assignment was carried out using Pangolin.<sup>9</sup> Detection of  
145 amino acid changes as compared to the original Wuhan strain was done using COV-  
146 GLUE.<sup>10</sup> Maximum likelihood phylogenetic tree was reconstructed using IQ-TREE.<sup>11</sup>

#### 147 **SARS-CoV-2 antibody measurement**

148 We measured antibodies against SARS-CoV-2 nucleocapsid (N) protein using Elecsys  
149 Anti-SARS-CoV-2 assay (Diagnostics, Germany), and SARS-CoV-2 neutralizing  
150 antibodies using SARS-CoV-2 Surrogate Virus Neutralization Test (sVNT) (GenScript,  
151 USA).<sup>12</sup> The experiments were carried according to the manufacturers' instructions.

#### 152 **Additional data for analysis**

153 Because the breakthrough infections coincided with the sampling schedule at month 3 after  
154 dose 1 (week 7 after the second dose) of the vaccine study,<sup>6</sup> we used available data on  
155 neutralizing antibodies of the vaccine study for case-control analyses. We matched cases  
156 with the controls for age and gender with a matching ratio of 1:3 (when data of the controls  
157 are available) or 1:1 (when data of the controls are limited).

158 For viral load comparison, we used previously reported data of SARS-CoV-2 infected  
159 cases detected in Vietnam during the early phase of the pandemic in Vietnam between  
160 March and April 2020.<sup>5</sup>

#### 161 **Data analysis**

162 Data analysis was carried in Graphpad Prims 9.0.2. For comparisons between groups, we  
163 used the Fisher exact test or the Mann-Whitney U test. We performed linear regression  
164 analysis to assess the correlation between neutralizing antibody levels at diagnosis and  
165 peak viral loads.

#### 166 **Ethics**

167 The study was approved by the Institutional Review Board of HTD and the Oxford  
168 Tropical Research Ethics Committee, University of Oxford, UK. Written informed  
169 consents were obtained from all the participants.

## 170 **RESULTS**

### 171 **The outbreak and initial investigations**

172 On 11<sup>th</sup> June 2021 (week 7 after the second dose), a 41-year old member of HTD staff  
173 (patient 1) complained of body pain and tiredness. Because community transmission of  
174 SARS-CoV-2 has been increasing in HCMC since May 2021, he was tested that day and  
175 found to be positive for SARS-CoV-2 (PCR Ct value: 18.5 (equivalent to log<sub>10</sub> viral load  
176 of 8.5 copies per mL)). PCR screening for SARS-CoV-2 was then expanded to all hospital  
177 staff and was completed by the end of 12<sup>th</sup> June 2021. A total of 52 additional members  
178 were found positive, including all 6 members sharing an office with patient 1 (Figure 1 and  
179 Supplementary Figure 1).

180 Following Vietnamese Government recommendations, HTD was locked down for two  
181 weeks (12<sup>th</sup>-26<sup>th</sup> June 2021), with no one allowed to enter or leave the hospital. Further  
182 PCR testing of all staff during this period identified 16 additional positive cases, totaling  
183 69 infected members from 19/34 departments (Figure 1 and Supplementary Table 1).  
184 Serological testing for SARS-CoV-2 N protein antibodies was carried out on 683 members  
185 (including those stayed in the HTD during the lockdown and the infected cases) between  
186 14<sup>th</sup> and 16<sup>th</sup> June 2021, but none was positive.

### 187 **Demographics and clinical features**

188 All the 69 members of HTD staff infected with SARS-CoV-2 were isolated for clinical  
189 follow up and management at HTD. Apart from patient 1, one additional member

190 presented with symptoms at diagnosis (15<sup>th</sup> June 2021). Thus only 1 out of the first 53  
191 members tested positive between 11<sup>th</sup> and 12<sup>th</sup> June 2021 was symptomatic at diagnosis.  
192 Sixty-two consented to have their demographics and clinical features reported. Of these,  
193 two received one dose, and 60 (including patient 1) were fully vaccinated. The infected  
194 cases (29 females and 33 males) were aged between 24-60 years (median 41.5 years).  
195 Forty-seven developed respiratory symptoms between 1-15 days (median: 4) after  
196 diagnosis. Three had pneumonia on chest x-ray examination. Of these, one required  
197 oxygen supplementation for three days. Otherwise, they all were either asymptomatic or  
198 mildly symptomatic (Table 1). All those with symptoms recovered uneventfully.

### 199 **Viral loads**

200 At diagnosis, median PCR Ct value was 31.7 (range: 37.6–14.0), equivalent to log<sub>10</sub> copies  
201 per mL of 4.5 (range: 2.6–9.9); eleven (20.8%) of the first 53 cases from 5 different  
202 departments had high viral loads, median Ct value (range): 17.9 (14.0–22.6), equivalent to  
203 log<sub>10</sub> copies per mL of 8.7 (range: 7.3–9.9), including patient 1 and 4/6 members sharing  
204 the office with him.

205 The viral loads of the 49 (pre)symptomatic cases peaked within 2-3 days before and after  
206 symptom onset, with a median Ct value (range) of 16.8 (13.1–36.9), corresponding to log<sub>10</sub>  
207 copies per mL of 9.1 (range: 2.8–10.2) (Figure 2A). During the course of infection, peaks  
208 of viral loads measured at any time point of the symptomatic cases were higher than that of  
209 asymptomatic cases; 16.5 (13.6–32) vs. 30.8 (13.1–36.9), equivalent to median log<sub>10</sub> viral  
210 load of 9.2 copies per mL (range: 4.3–10.1) vs. 4.7 copies per mL (range: 2.8–10.2),  
211 p=0.005, respectively (Supplementary Figure 2). The median time from diagnosis to PCR  
212 negative prior discharge was 21 days (range: 8–33).

213 Compared with peak viral loads of cases infected with old SARS-CoV-2 strains detected in  
214 Vietnam between March and April 2020, peak viral loads of breakthrough cases were  
215 significantly higher, median log<sub>10</sub> viral load in copies per mL (range): 9.1 (range: 2.8–  
216 10.2) vs. 6.7 (1.9–9.5), equivalent to 251 times higher for median viral loads. The  
217 differences were more profound among symptomatic cases while there was no difference  
218 in viral loads among asymptomatic cases between the two groups (Figure 2B).

### 219 **Whole genome sequencing**

220 A total of 23 whole genome sequences of SARS-CoV-2 were obtained from 35 samples  
221 with sufficient viral loads. The obtained sequences were derived from 23 members  
222 (including patient 1) of 10 different departments of HTD (Supplementary Table 1). All  
223 were assigned to SARS-CoV-2 Delta variant. They were either identical or different from  
224 each other by only 1 to 7 nucleotides, but no novel amino acid changes were identified  
225 among them. Phylogenetically, the 23 sequences clustered tightly together but were  
226 separated from the contemporary Delta variant sequences obtained from cases of  
227 community transmission in HCMC (Figure 3), suggestive of ongoing transmission between  
228 the vaccinated people.

### 229 **Antibody development and case-control analyses**

230 A total of 209 plasma samples were collected from the 62 study participants; 61 at  
231 diagnosis and week 1, and 57 at week 2 and 31 at week 3 after admission. At diagnosis, all  
232 but three had detectable neutralizing antibodies, with comparable levels between  
233 (pre)symptomatic and asymptomatic cases (Supplementary Figure 3). Likewise, there was  
234 no correlation between neutralizing antibodies at diagnosis and peak viral loads during the  
235 course of infection (Figure 4).

236 At week 2 and 3 after diagnosis, neutralizing antibody levels of the case patients  
237 significantly increased, and were higher than neutralizing antibody levels measured at  
238 week 2 after the second dose of the 62 matched uninfected controls (Supplementary Figure  
239 3).

240 Ten patients had data on neutralizing antibodies measured at both two weeks after the  
241 second dose and at diagnosis. Neutralizing antibody levels measured at these two time  
242 points of the 10 case patients were significantly lower than those in the 30 matched  
243 uninfected controls, median % of inhibition (range): 69.4 (13.7-96.3) vs. 91.3 (57.5-97.6),  
244  $p=0.012$  and 59.4 (12.5-95.0) vs. 91.1 (20.9-97.0),  $p=0.001$ , respectively (Figure 5).  
245 Similarly, the 62 case patients had lower levels of neutralizing antibodies measured at  
246 diagnosis than those in the 62 matched uninfected controls, median % of inhibition  
247 (range): 68.6 (12.5-97.0) vs. 82.3 (19.3-96.7),  $p=0.002$ .

248 The seroconversion rates for antibodies against N protein steadily increased from 0% at  
249 baseline to 65% (20/31) at week 3. Asymptomatic patients had slightly lower  
250 seroconversion rates than symptomatic patients (Supplementary Figure 4). There was no  
251 difference in neutralizing antibodies between the N protein antibody negative and positive  
252 groups (data not shown).

## 253 **DISCUSSION**

254 We studied Oxford-AstraZeneca vaccine breakthrough infections associated with SARS-  
255 CoV-2 Delta variant among healthcare workers of a major hospital for infectious diseases  
256 in HCMC, Vietnam between 11<sup>th</sup> and 25<sup>th</sup> June 2021 (week 7 and 8 after the second dose).  
257 62/69 infected cases participated in the clinical study. One required cannula oxygen  
258 supplementation for three days but all made full recovery in line with recent reports

259 regarding the vaccine effectiveness in protecting against severe disease.<sup>13-15</sup> However, we  
260 found strong evidence demonstrating for the first time that fully vaccinated healthcare  
261 workers could still pass the virus between each other.

262 Indeed, the 23 whole-genome sequences of SARS-CoV-2 obtained from the infected cases  
263 clustered tightly on the phylogenetic tree, but separately from the contemporary Delta  
264 variant genomes obtained from cases of community transmission in HCMC. This strongly  
265 suggested that these individuals likely caught the virus from a single introduction into the  
266 hospital. Additionally, because only 1 out of the first 53 infected cases of the outbreak  
267 were symptomatic at diagnosis, presymptomatic and/or asymptomatic transmission had  
268 occurred between the vaccinated members of staff of HTD. This was likely attributed to  
269 several factors. Firstly, high viral loads,  $>7 \log_{10}$  copies per mL, which was strongly  
270 correlated with positive culture (i.e. infectiousness),<sup>8,16</sup> was recorded in 11 of the first 53  
271 positive cases of the outbreak at diagnosis. Second, HTD offices are typically equipped  
272 with air conditioners without mechanical ventilation systems, a well-known indoor setting  
273 that could facilitate the transmission of SARS-CoV-2.<sup>17</sup> Third, mask wearing in the office  
274 was not mandatory at the time.

275 Lower levels of neutralizing antibodies after vaccination and at diagnosis were associated  
276 with breakthrough infections in a recent report from Israel,<sup>18</sup> supporting findings of the  
277 present study. However, we found no correlation between vaccine-induced neutralizing  
278 antibody levels at diagnosis and the development of respiratory symptoms or viral loads  
279 (i.e. infectivity). Thus, while neutralizing antibodies might be a surrogate of protection,  
280 especially against severe diseases as a whole,<sup>19</sup> they might not be good indicators of  
281 disease progression and infectiousness for breakthrough Delta variant infection. The rapid

282 increase in neutralizing antibodies after infection among cases of the present study in turn  
283 suggested that a third dose may improve the immunity and potentially the protection.

284 At the beginning of the outbreak, none of the HTD members of staff (including the PCR  
285 confirmed cases) were tested positive for N-protein antibodies, which only develop in  
286 response to whole-virus based vaccine and natural infection. Additionally, between 12<sup>th</sup>  
287 and 14<sup>th</sup> May 2021, all members of HTD staff were subjected to a periodic testing for  
288 SARS-CoV-2 by PCR, but none was positive. The data thus suggested that the infected  
289 cases were captured at an early phase of the infection. Therefore, by carefully following up  
290 the patients during hospitalization, we have also provided new insights into the natural  
291 history of breakthrough Delta variant infections. We found viral loads of breakthrough  
292 Delta variant infection cases peaked around 2-3 days before and after the development of  
293 symptoms, and were 251 times higher than those of the infected cases detected during the  
294 early phase of the pandemic in 2020.<sup>5</sup> Additionally, there has been only one report  
295 showing that 9/11 cases of vaccine breakthrough infection had no detectable RNA when  
296 retested within 2–7 days after diagnosis.<sup>20</sup> Yet, we found prolonged PCR positivity was up  
297 to 33 days in our study participants. These factors might explain the current rapid  
298 expansion of the Delta variant, even in the countries with high vaccination coverage.

299 In summary, we report the transmission SARS-CoV-2 Delta variant among vaccinated  
300 health care workers. Breakthrough Delta variant infections are associated with high viral  
301 loads, prolonged PCR positivity, and low levels of neutralizing antibodies after vaccination  
302 and at diagnosis. These factors coupled with poorly ventilated indoor settings and without  
303 mask wearing might have facilitated presymptomatic and/or asymptomatic transmission  
304 among the vaccinated workers. Physical distancing measures remain critical to reduce

305 SARS-CoV-2 Delta variant transmission, thereby mitigating the impact of the ongoing  
306 COVID-19 pandemic.

Preprint not peer reviewed



307 **ACKNOWLEDGEMENTS**

308 This study was funded by the Wellcome Trust of Great Britain (106680/B/14/Z and  
309 204904/Z/16/Z).

310 We thank our colleagues at the Hospital for Tropical Diseases in Ho Chi Minh City,  
311 Vietnam for their participations in this study and for their logistic support with the data  
312 collection. We thank Ms Le Kim Thanh for her logistics support.

313

314 **OUCRU COVID-19 Research Group**

315 **Hospital for Tropical Diseases, Ho Chi Minh City, Vietnam:** Nguyen Van Vinh Chau,  
316 Nguyen Thanh Dung, Le Manh Hung, Huynh Thi Loan, Nguyen Thanh Truong, Nguyen  
317 Thanh Phong, Dinh Nguyen Huy Man, Nguyen Van Hao, Duong Bich Thuy, Nghiem My  
318 Ngoc, Nguyen Phu Huong Lan, Pham Thi Ngoc Thoa, Tran Nguyen Phuong Thao, Tran  
319 Thi Lan Phuong, Le Thi Tam Uyen, Tran Thi Thanh Tam, Bui Thi Ton That, Huynh Kim  
320 Nhung, Ngo Tan Tai, Tran Nguyen Hoang Tu, Vo Trong Vuong, Dinh Thi Bich Ty, Le  
321 Thi Dung, Thai Lam Uyen, Nguyen Thi My Tien, Ho Thi Thu Thao, Nguyen Ngoc Thao,  
322 Huynh Ngoc Thien Vuong, Huynh Trung Trieu Pham Ngoc Phuong Thao, Phan Minh  
323 Phuong

324 **Oxford University Clinical Research Unit, Ho Chi Minh City, Vietnam:** Dong Thi  
325 Hoai Tam, Evelyne Kestelyn, Donovan Joseph, Ronald Geskus, Guy Thwaites, Ho Quang  
326 Chanh, H. Rogier van Doorn, Ho Van Hien, Ho Thi Bich Hai, Huynh Le Anh Huy, Huynh  
327 Ngan Ha, Huynh Xuan Yen, Jennifer Van Nuil, Jeremy Day, Katrina Lawson, Lam Anh  
328 Nguyet, Lam Minh Yen, Le Dinh Van Khoa, Le Nguyen Truc Nhu, Le Thanh Hoang Nhat,  
329 Le Van Tan, Sonia Lewycka Odette, Louise Thwaites, Marc Choisy, Mary Chambers,  
330 Motiur Rahman, Ngo Thi Hoa, Nguyen Thanh Thuy Nhien, Nguyen Thi Han Ny, Nguyen  
331 Thi Kim Tuyen, Nguyen Thi Phuong Dung, Nguyen Thi Thu Hong, Nguyen Xuan Truong,  
332 Phan Nguyen Quoc Khanh, Phung Le Kim Yen, Phung Tran Huy Nhat, Sophie Yacoub,  
333 Thomas Kesteman, Nguyen Thuy Thuong Thuong, Tran Tan Thanh, Vu Thi Ty Hang

334 **REFERENCES**

- 335 1. Bolze A, Cirulli ET, Luo S, White S, Wyman D, Dei Rossi A, Cassens T, Jacobs S,  
336 Nguyen J, Ramirez JM, et al. Rapid displacement of SARS-CoV-2 variant B.1.1.7 by  
337 B.1.617.2 and P.1 in the United States. *medRxiv* 2021.
- 338 2. Wall EC, Wu M, Harvey R, Kelly G, Warchal S, Sawyer C, Daniels R, Hobson P,  
339 Hatipoglu E, Ngai Y, et al. Neutralising antibody activity against SARS-CoV-2 VOCs  
340 B.1.617.2 and B.1.351 by BNT162b2 vaccination. *The Lancet* 2021.
- 341 3. Zhou D, Dejnirattisai W, Supasa P, Liu C, Mentzer AJ, Ginn HM, Zhao Y,  
342 Duyvesteyn HME, Tuekprakhon A, Nutalai R, et al. Evidence of escape of SARS-CoV-2  
343 variant B.1.351 from natural and vaccine-induced sera. *Cell* 2021; **184**(9): 2348-61.e6.
- 344 4. Farinholt T, Doddapaneni H, Qin X, Menon V, Meng Q, Metcalf G, Chao H,  
345 Gingras MC, Farinholt P, Agrawal C, et al. Transmission event of SARS-CoV-2 Delta  
346 variant reveals multiple vaccine breakthrough infections. *medRxiv* 2021.

- 347 5. Chau NVV, Thanh Lam V, Thanh Dung N, Yen LM, Minh NNQ, Hung LM, Ngoc  
348 NM, Dung NT, Man DNH, Nguyet LA, et al. The natural history and transmission  
349 potential of asymptomatic SARS-CoV-2 infection. *Clin Infect Dis* 2020.
- 350 6. Chau NVV, Nguyet LA, Truong NT, Toan LM, Dung NT, Hung LM, Nhan MT,  
351 Man DNH, Ngoc NM, Thao HP, et al. Immunogenicity of Oxford-AstraZeneca COVID-19  
352 vaccine in Vietnamese healthcare workers *MedRxiv* 2021.
- 353 7. Corman VM, Landt O, Kaiser M, Molenkamp R, Meijer A, Chu DKW, Bleicker T,  
354 Brünink S, Schneider J, Schmidt ML, et al. Detection of 2019 novel coronavirus (2019-  
355 nCoV) by real-time RT-PCR. *Eurosurveillance* 2020; **25**(3).
- 356 8. Jones TC, Biele G, Muhlemann B, Veith T, Schneider J, Beheim-Schwarzbach J,  
357 Bleicker T, Tesch J, Schmidt ML, Sander LE, et al. Estimating infectiousness throughout  
358 SARS-CoV-2 infection course. *Science* 2021; **373**(6551).
- 359 9. Rambaut A, Holmes EC, O'Toole A, Hill V, McCrone JT, Ruis C, du Plessis L,  
360 Pybus OG. A dynamic nomenclature proposal for SARS-CoV-2 lineages to assist genomic  
361 epidemiology. *Nat Microbiol* 2020; **5**(11): 1403-7.
- 362 10. Singer J, Gifford R, Cotten M, Robertson D. CoV-GLUE: A Web Application for  
363 Tracking SARSCoV-2 Genomic Variation. *Preprint* 2020.
- 364 11. Nguyen LT, Schmidt HA, von Haeseler A, Minh BQ. IQ-TREE: a fast and  
365 effective stochastic algorithm for estimating maximum-likelihood phylogenies. *Mol Biol*  
366 *Evol* 2015; **32**(1): 268-74.
- 367 12. Tan CW, Chia WN, Qin X, Liu P, Chen MI, Tiu C, Hu Z, Chen VC, Young BE,  
368 Sia WR, et al. A SARS-CoV-2 surrogate virus neutralization test based on antibody-  
369 mediated blockage of ACE2-spike protein-protein interaction. *Nat Biotechnol* 2020; **38**(9):  
370 1073-8.
- 371 13. Stowe J, Andrews N, Gower C, Gallagher E, Utsi L, Simmons R, Thelwall S,  
372 Tessier E, Groves N, Dabrera G, et al. Effectiveness of COVID-19 vaccines against  
373 hospital admission with the Delta (B.1.617.2) variant. *Preprint* 2021.
- 374 14. Bernal JL, Andrews N, Gower C, Gallagher E, Simmons R, Thelwall S, Stowe J,  
375 Tessier E, Groves N, Dabrera G, et al. Effectiveness of COVID-19 vaccines against the  
376 B.1.617.2 variant. *MedRxiv* 2021.
- 377 15. Lopez Bernal J, Andrews N, Gower C, Gallagher E, Simmons R, Thelwall S,  
378 Stowe J, Tessier E, Groves N, Dabrera G, et al. Effectiveness of Covid-19 Vaccines  
379 against the B.1.617.2 (Delta) Variant. *New England Journal of Medicine* 2021.
- 380 16. van Kampen JJA, van de Vijver D, Fraaij PLA, Haagmans BL, Lamers MM, Okba  
381 N, van den Akker JPC, Endeman H, Gommers D, Cornelissen JJ, et al. Duration and key  
382 determinants of infectious virus shedding in hospitalized patients with coronavirus disease-  
383 2019 (COVID-19). *Nat Commun* 2021; **12**(1): 267.
- 384 17. Prevention CfDca. Scientific Brief: SARS-CoV-2 Transmission.  
385 [https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/sars-cov-2-](https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/sars-cov-2-transmission.html)  
386 [transmission.html](https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/sars-cov-2-transmission.html) 2021.
- 387 18. Bergwerk M, Gonen T, Lustig Y, Amit S, Lipsitch M, Cohen C, Mandelboim M,  
388 Gal Levin E, Rubin C, Indenbaum V, et al. Covid-19 Breakthrough Infections in  
389 Vaccinated Health Care Workers. *The New England journal of medicine* 2021.
- 390 19. Khoury DS, Cromer D, Reynaldi A, Schlub TE, Wheatley AK, Juno JA, Subbarao  
391 K, Kent SJ, Triccas JA, Davenport MP. Neutralizing antibody levels are highly predictive  
392 of immune protection from symptomatic SARS-CoV-2 infection. *Nat Med* 2021.

393 20. Brinkley-Rubinstein L, Peterson M, Martin R, Chan P, Berk J. Breakthrough  
394 SARS-CoV-2 Infections in Prison after Vaccination. *The New England journal of medicine*  
395 2021.

## 396 LEGENDS TO TABLES AND FIGURES

397 **Table 1:** Demographics and clinical characteristics of the study participants

398 **Figure 1:** Flowchart showing timelines and results of SARS-CoV-2 RT-PCR screening  
399 before and during the lockdown (11-25 June 2021)

400 **Notes to Figure 1:** \*The remaining members of staff were working from home.

401 **Figure 2:** Viral load analyses, A) plot outlining kinetics of viral loads in relation to illness  
402 onset of the 49 study participants who were either symptomatic or presymptomatic at  
403 admission, B) comparison between peak viral loads of breakthrough infections (cases) and  
404 those (controls) infected with old SARS-CoV-2 strains detected between March and April  
405 2020 in Vietnam

406 **Notes to Figure 2:** Vertical dashed line indicates the time point of illness onset. Horizontal  
407 dashed line indicates detection limit of PCR assay. A) Black lines indicates median viral  
408 loads, B) black dots represent for whole groups, red dots represent for symptomatic cases  
409 and blue dots represent for asymptomatic cases. Peak viral loads comparison between  
410 symptomatic and asymptomatic groups of the cases and controls: median  $\log_{10}$  viral load in  
411 copies per mL (range): 9.2 (4.3–10.1) vs. 6.9 (3.7–9.5),  $p < 0.001$  and 4.7 (2.8–10.2) vs. 4.9  
412 (1.9–8.6),  $p = 0.511$ .

413 **Figure 3:** Maximum likelihood tree illustrating the relatedness between SARS-CoV-2  
414 Delta variant strains obtained from cases of vaccine breakthrough infection (red) and  
415 contemporary Delta variant sequences obtained from cases of community transmission in  
416 Ho Chi Minh City (blue) and other provinces in Vietnam or countries (black).

417 **Note to Figure 3:** Cases of vaccine breakthrough infections were derived from 12/19  
418 affected department of the Hospital for Tropical Diseases

419 **Figure 4:** Correlation between neutralizing antibodies at diagnosis and peak viral loads  
420 during the course of infection

421 **Figure 5:** Comparison between neutralizing antibody levels of case patients (red) and  
422 uninfected controls (grey green). A) between the 10 case patients whose data on  
423 neutralizing antibodies at both week 2 after the second doses (8 weeks after the first dose)  
424 abd at diagnosis were available and the uninfected controls, B) between the 62 case  
425 patients and the uninfected controls for data at diagnosis

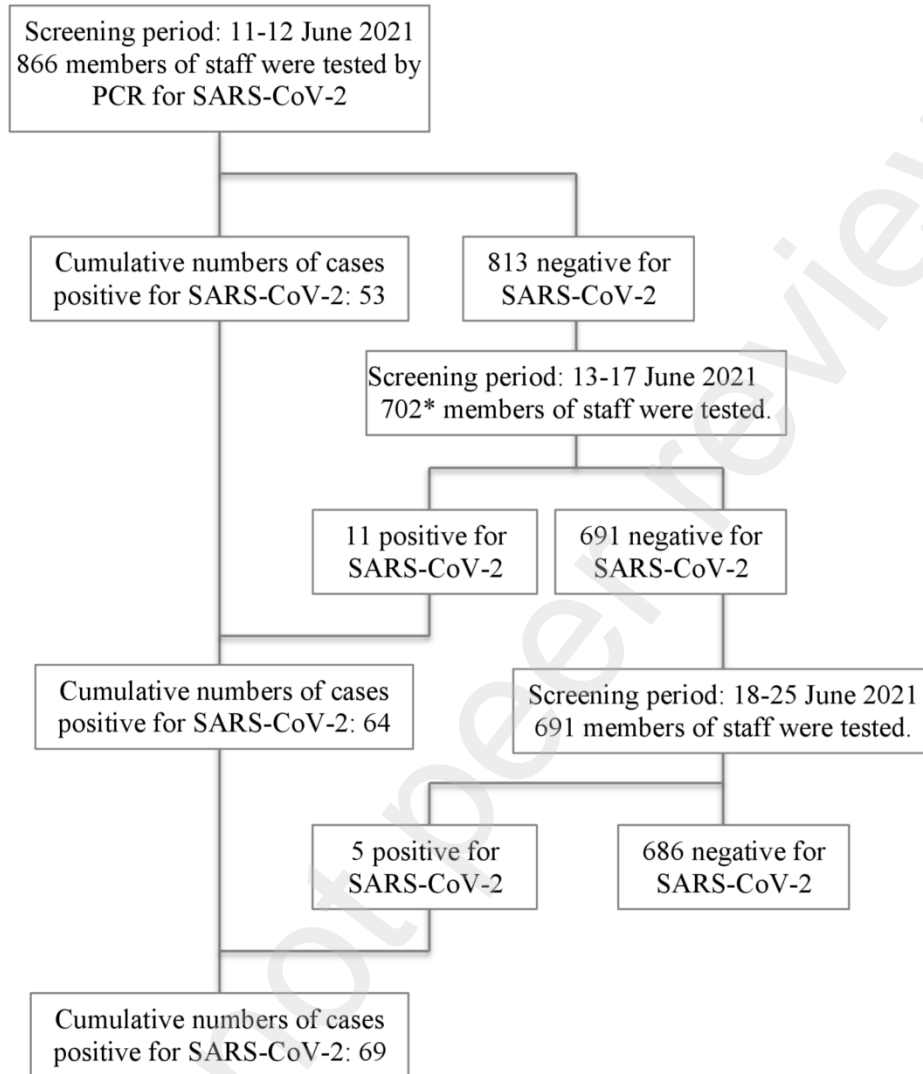
**Table 1:** Demographics and clinical characteristics of the study participants

Signs/Symptoms	All cases (n=62)	Male (n=33)	Female (n=29)
Age, y, median (range)	41.5 (24-60)	41 (27-60)	43 (24-59)
Occupation, n (%)			
Nurse	13	5	8
Pharmacist	10	3	7
IT	7	7	0
Clinician	7	5	2
Accountant	4	0	4
Technical staff	3	3	0
Cleaner	2	2	0
Others	16	8	8
Symptomatic, n (%)	49 (79.0)	24 (72.7)	25 (86.2)
PCR diagnosis to illness onset, d, (median; range)*	4 (0-15)	3 (0-8)	5 (0-15)
Comorbidity <sup>#</sup> , n (%)	17 (27.4)	9 (27.3)	8 (27.6)
COVID-19 vaccination <sup>‡</sup> , n (%)	62 (100)	33 (100)	29 (100)
Two doses	60 (96.7)	33 (100)	27 (93.1)
One dose	2 (3.3)	0	2 (6.9)
Fever, n (%)	17 (27.4)	9 (27.3)	8 (27.6)
Cough, n (%)	23 (37.1)	19 (57.6)	14 (48.3)
Sore throat, n (%)	21 (33.9)	9 (27.3)	12 (41.4)
Runny nose, n (%)	22 (35.5)	9 (27.3)	13 (44.8)
Loss of smell, n (%)	24 (38.7)	14 (42.4)	10 (34.5)
Loss of taste, n (%)	5 (8.1)	3 (9.1)	2 (6.9)
Muscle pain, n (%)	17 (27.4)	13 (39.4)	4 (13.8)
Headache, n (%)	12 (19.4)	6 (18.2)	6 (20.7)
Chest pain, n (%)	2 (3.2)	0	2 (6.9)
Nausea, n (%)	5 (8.1)	3 (9.1)	2 (6.9)
Others, n (%) <sup>§</sup>	5 (8.1)	1 (3.0)	4 (13.8)
Pneumonia, n (%) <sup>**</sup>	3 (4.8)	0	3 (10.3)

**Notes to Table 1:**

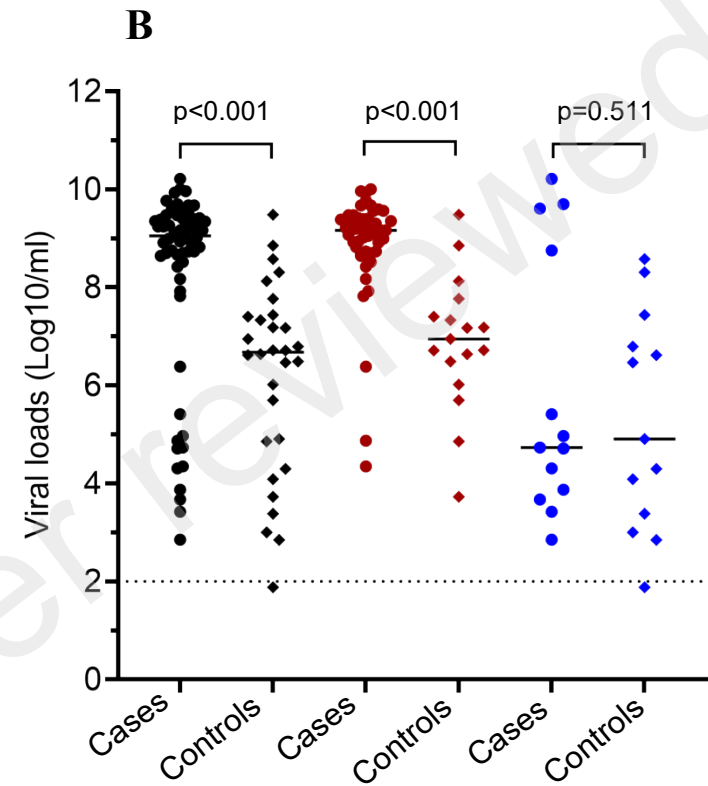
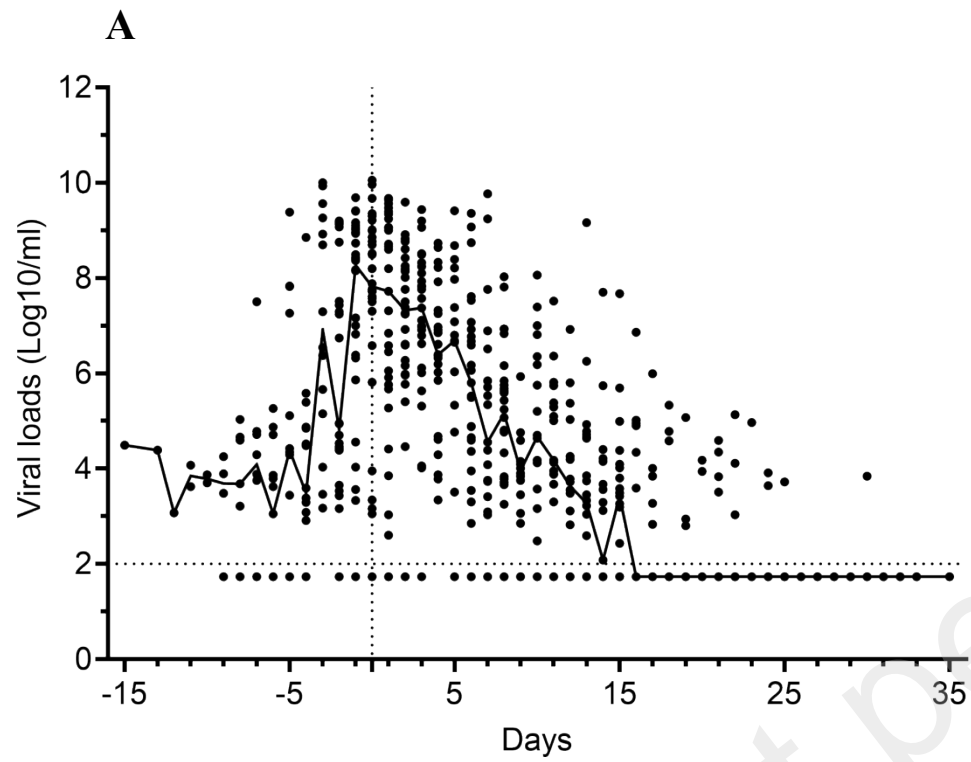
\*Symptomatic cases only

<sup>‡</sup>All receiving AstraZeneca vaccine; The second doses were given in last 2 weeks of April 2021.<sup>#</sup>Overweight (n=6), obese (n=3), hypertension (n=3), hepatitis B (n=2), diabetes (n=1), pregnancy (n=1), diabetes and hepatitis B (n=1).<sup>§</sup>Chills (n=2), sweating (n=1), giddiness (n=1), red eyes (n=1), and diarrhea (n=1)<sup>\*\*</sup>One requiring oxygen supplementation via cannula route for 3 days.



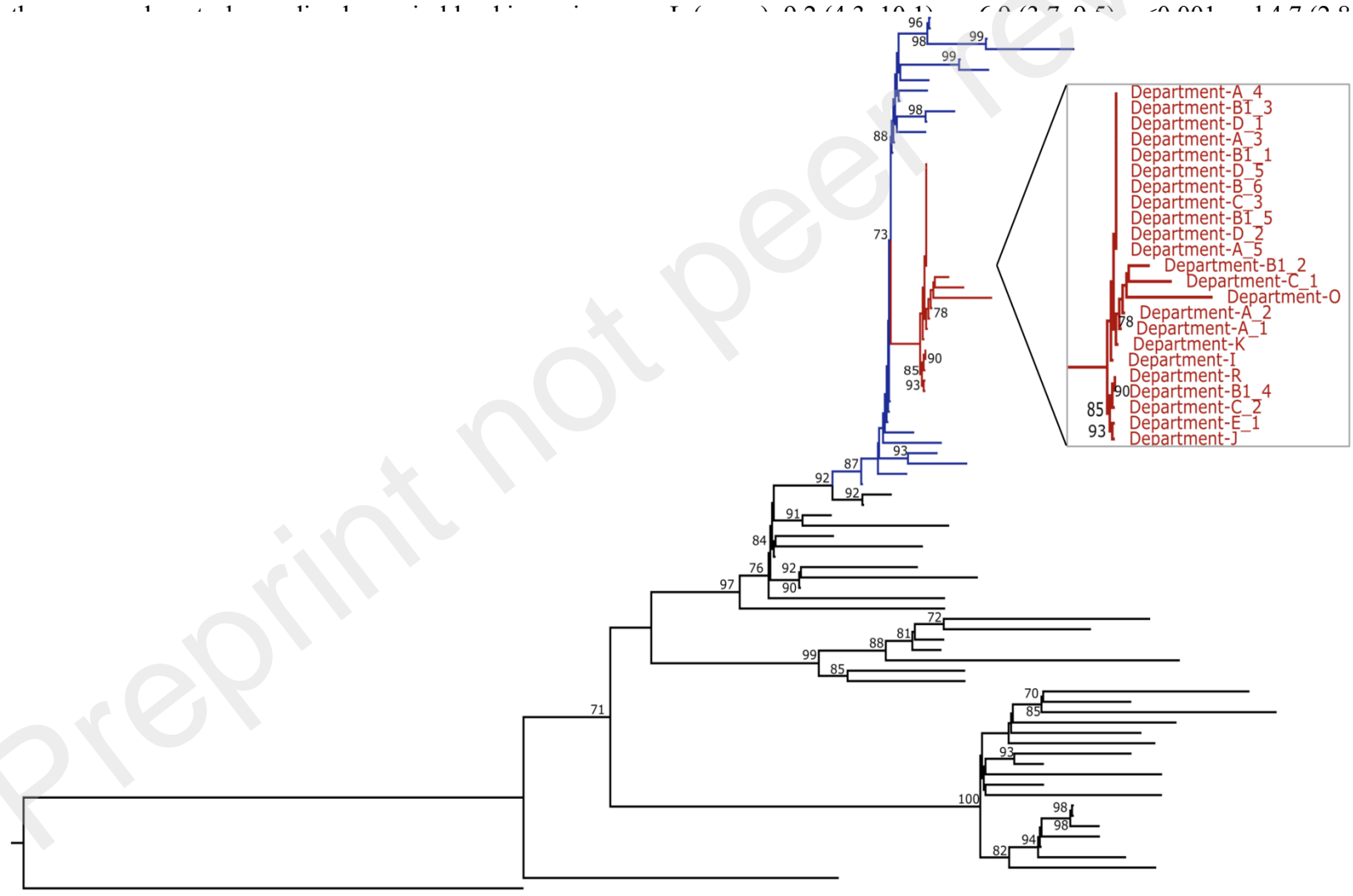
**Figure 1:** Flowchart showing timelines and results of SARS-CoV-2 RT-PCR screening before and during the lockdown (11-25 June 2021)

**Notes to Figure 1:** \*The remaining members of staff were working from home.



**Figure 2:** Viral load analyses, A) plot outlining kinetics of viral loads in relation to illness onset of the 49 study participants who were either symptomatic or presymptomatic at admission, B) comparison between peak viral loads of breakthrough infections (cases) and those (controls) infected with old SARS-CoV-2 strains detected between March and April 2020 in Vietnam

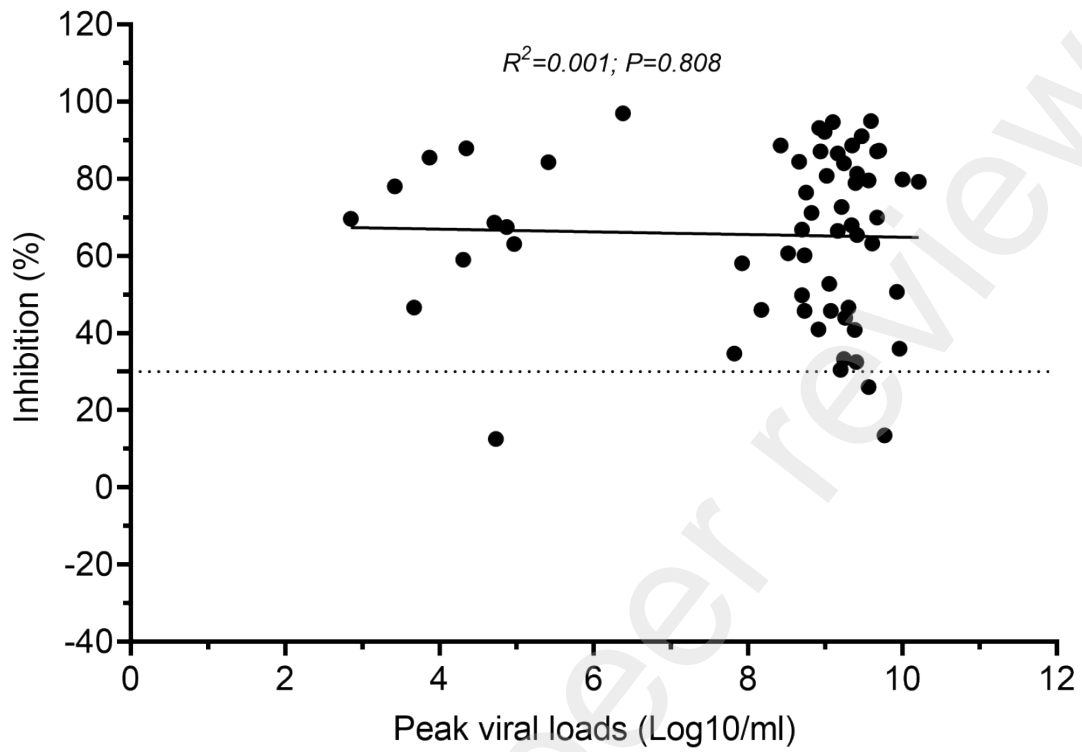
**Notes to Figure 2:** Vertical dashed line indicates the time point of illness onset. Horizontal dashed line indicates detection limit of PCR assay. A) Black lines indicates median viral loads, B) black dots represent for whole groups, red dots represent for symptomatic cases and blue dots represent for asymptomatic cases. Peak viral loads comparison between symptomatic and asymptomatic groups of 1.0E+07 (1.3E+07-1.4E+07) (1.0E+07-1.3E+07) (1.0E+07-1.3E+07) (1.0E+07-1.3E+07) (1.0E+07-1.3E+07) (1.0E+07-1.3E+07) (1.0E+07-1.3E+07) (1.0E+07-1.3E+07) (1.0E+07-1.3E+07) (1.0E+07-1.3E+07)



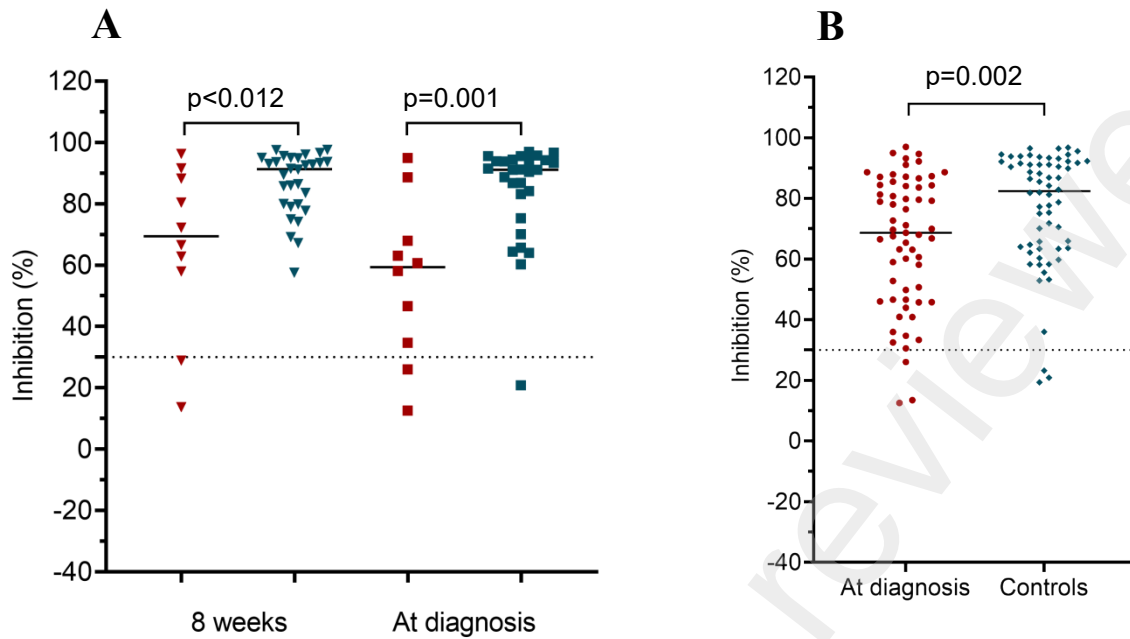
**Figure 3:** Maximum likelihood tree illustrating the relatedness between SARS-CoV-2 Delta variant strains obtained from cases of vaccine breakthrough infection (red) and contemporary Delta variant sequences obtained from cases of community transmission in Ho Chi Minh City (blue) and other provinces in Vietnam or countries (black).

**Note to Figure 3:** Cases of vaccine breakthrough infections were derived from 12/19 affected department of the Hospital for Tropical Diseases





**Figure 4:** Correlation between neutralizing antibodies at diagnosis and peak viral loads during the course of infection

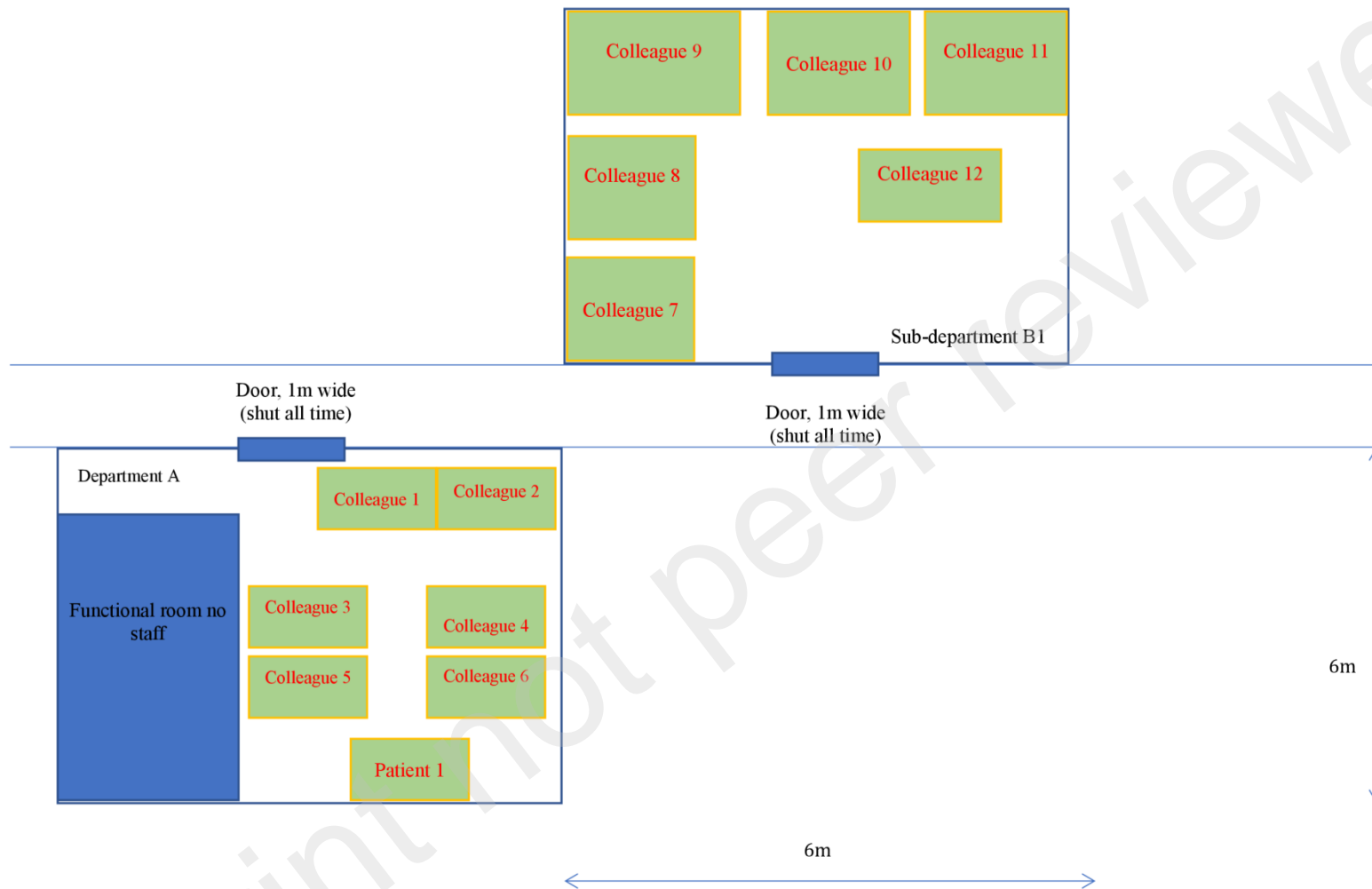


**Figure 5:** Comparison between neutralizing antibody levels of case patients (red) and uninfected controls (grey green). A) between the 10 case patients whose data on neutralizing antibodies at both week 2 after the second doses (8 weeks after the first dose) and at diagnosis were available and the uninfected controls, B) between the 62 case patients and the uninfected controls for data at diagnosis

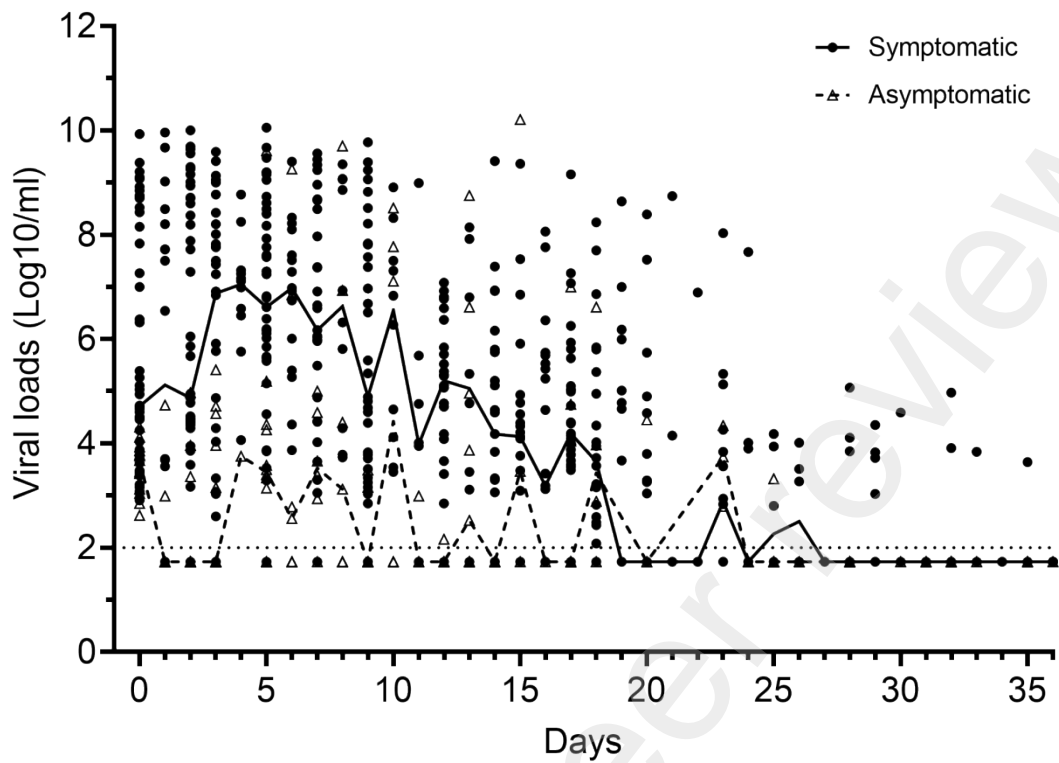
## SUPPLEMENTARY MATERIALS

**Supplementary Table 1:** Numbers of PCR confirmed cases detected per department

Name of department*	Functions	Number of staff	Number of staff tested positive (%)	Numbers genomes obtained
Department A	Supportive service	7	7 (100)	5
Department B	Supportive service	56	16 (29)	6
Sub-department B1	Supportive service	8	7 (88)	6
Sub-department B2	Supportive service	7	4 (57)	0
Sub-department B3	Supportive service	8	3 (38)	0
Sub-department B4	Supportive service	9	2 (22)	0
Department C	Supportive service	3	3 (100)	3
Department D	Supportive service	60	12 (20)	3
Department E	Patient care	75	6 (8)	1
Department F	Supportive service	36	4 (11)	0
Department G	Patient care	50	3 (6)	0
Department H	Supportive service	20	3 (15)	0
Department I	Supportive service	6	2 (33)	1
Department J	Patient care	28	1 (4)	1
Department K	Patient care	31	1 (3)	1
Department L	Patient care	32	1 (3)	0
Department N	Patient care	28	1 (4)	0
Department O	Patient care	19	1 (5)	1
Department P	Patient care	29	1 (3)	0
Department Q	Supportive service	11	1 (9)	0
Department R	Supportive service	15	1 (7)	1
Department S	Patient care	17	1 (5.9)	0
Department T	Patient care	18	1 (5.6)	0

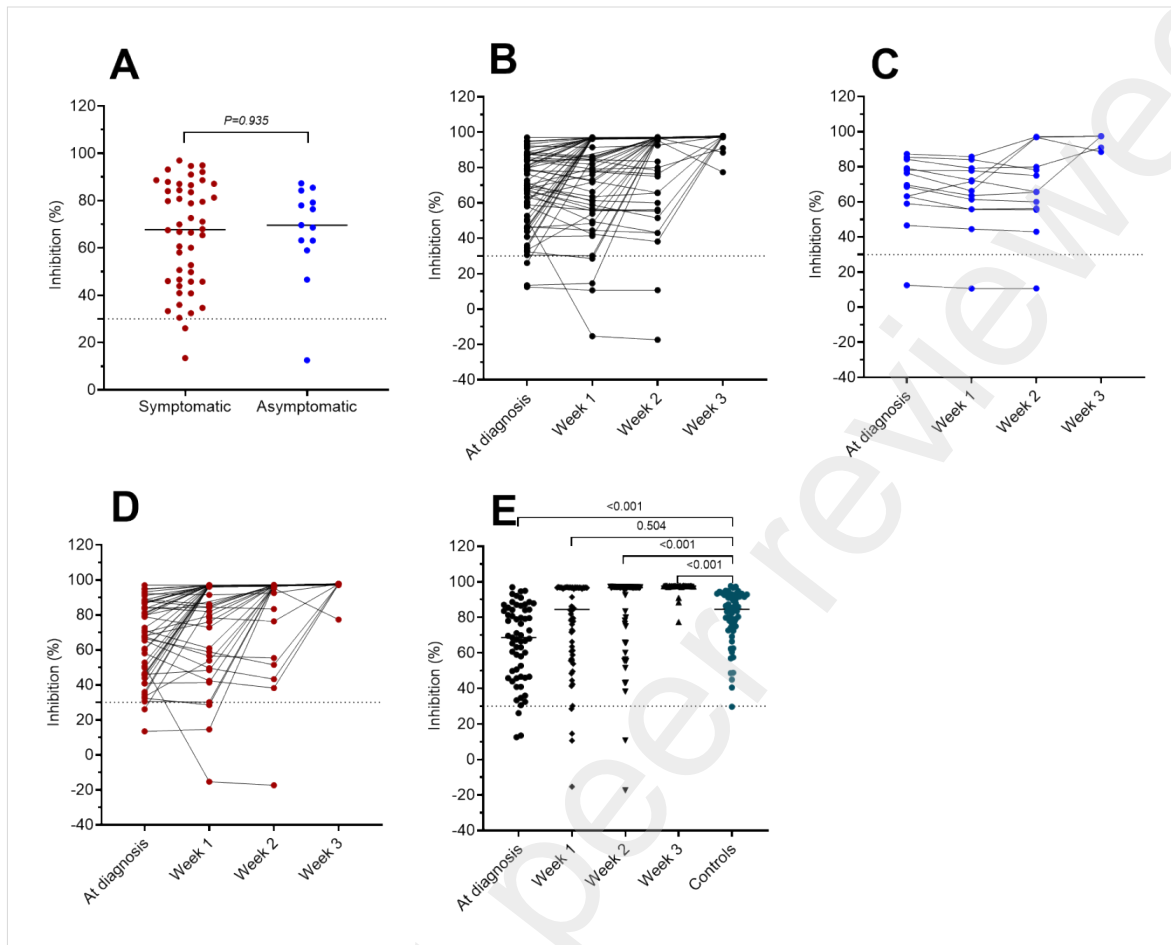


**Supplementary Figure 1:** Layout of office of patient 1 and a close office where 7/8 members were tested positive on 11<sup>th</sup>-12<sup>th</sup> June 2021. Office names are linked with Supplementary Table 1. Offices are equipped with air conditioners without mechanical ventilation. During working hours, doors are kept closed to maintain cooling air.



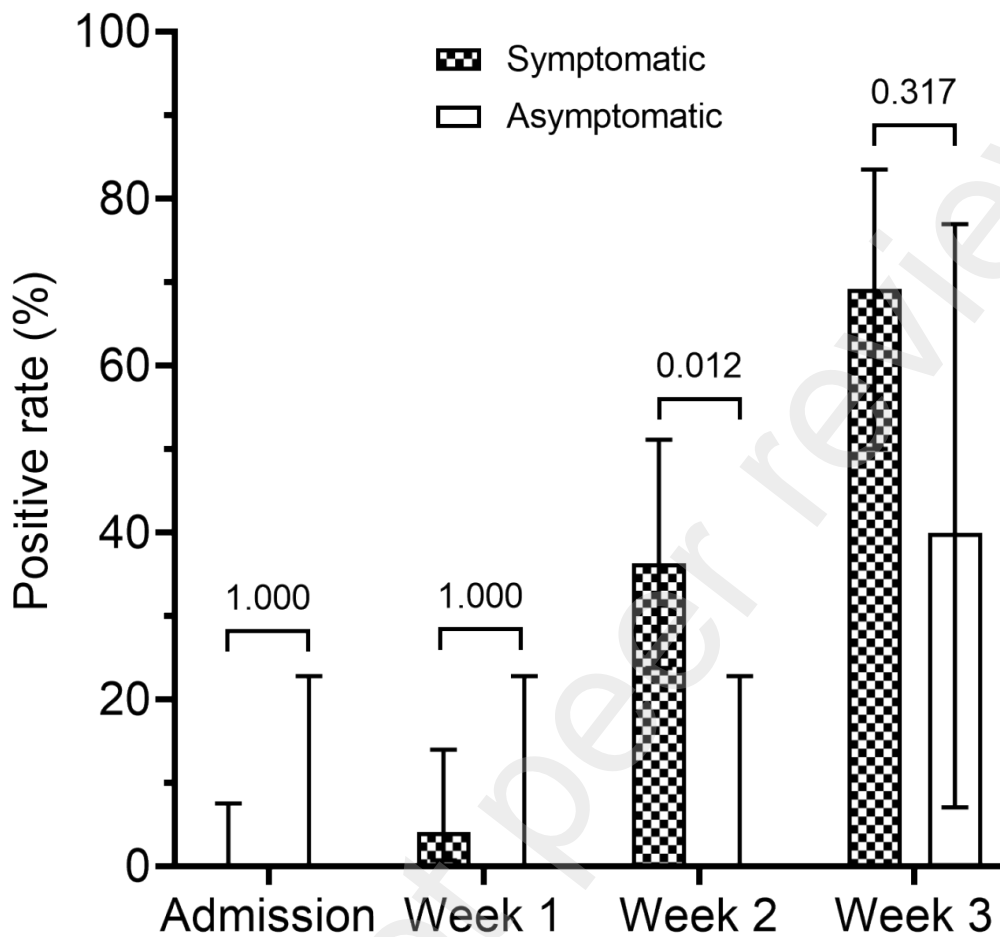
**Supplementary Figure 2:** Plot outlining kinetics of viral loads since PCR diagnosis during the course of hospitalization of the asymptomatic and symptomatic cases

**Notes to Supplementary Figure 2:** (Dashed) lines indicate median viral loads.



**Supplementary Figure 3:** Results of neutralizing antibody measurement, A) at diagnosis of symptomatic (including those developed symptoms after diagnosis) and asymptomatic cases, and kinetics of neutralizing antibodies at admission and at week 1, 2 and 3 after admission of B) the whole group, C) the asymptomatic group, D) the symptomatic group, and E) in comparison with the control group

**Supplementary Notes to Figure 3:** Dashed line indicates assay cut-off (30%). The asymptomatic case (panel C) who remained seronegative during infection did not respond to the vaccine (data not shown). Neutralizing antibody measurement were repeated twice for the symptomatic case who became seronegative at week 1 and week 2. Age and gender comparison between cases and controls: median in years (range): 41.5 (24-60) vs. 37.5 (24-58),  $p=0.47$ , and male/female 33/29 vs. 23/29,  $p=0.07$ .



**Supplementary Figure 4:** Seroconversion rates against N protein at admission, and week 1, 2 and 3 after admission.

**Note to Supplementary Figure 4:** For the whole group, the seroconversion rates for antibodies against N protein increased from 0% at baseline to 3.3% (2/61) at week 1, 28.1% (16/57) at week 2 and 65% (20/31) at week 3.