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

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ABSTRACT

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

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

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

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

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RESEARCH IN CONTEXT

Evidence before this study

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

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

Added value of this study

We studied 62 breakthrough cases among healthcare workers of a major hospital for infectious diseases in Ho Chi Minh City (HCMC), Vietnam between 11th-25 June 2021. We captured the infected cases at a very early phase of the infection and carefully followed them up during hospitalization to assess the kinetic of viral loads and neutralizing antibodies, and the development of clinical symptoms. To dissect the epidemiological link and the transmission potential between the vaccinated healthcare workers, we conducted whole genome sequencing of SARS-CoV-2.

49/62 case patients were (pre)symtomatic) and all recovered uneventfully. A total of 23 complete genome sequences were obtained from the breakthrough cases. The obtained sequences were all belonged to the Delta variant, but distinct from contemporary sequences obtained from cases of community transmission in HCMC, suggesting that the ongoing transmission had occurred between vaccinated healthcare workers. Viral loads peaked at around 2-3 days before and after the development of clinical symptoms with prolonged PCR positivity of up to 33 days. Viral loads were 251 times higher than those in cases infected with old SARS-CoV-2 strains detected in Vietnam between March and April 2020. Vaccine-induced neutralizing antibodies after the second dose and at diagnosis were lower than those in the matched uninfected controls. There was no correlation between vaccine-induced neutralizing antibody levels and viral loads (i.e. infectivity) or the development of symptoms during the course of infection.

Implications of all the available evidence

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

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

INTRODUCTION

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

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

MATERIALS AND METHODS

Setting

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

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

Data collection

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

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

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

Whole genome sequencing and sequence analysis

Whole-genome sequences of SARS-CoV-2 were directly obtained from leftover RNA after PCR testing using ARTIC protocol and Illunina reagents on a MiSeq platform with the inclusion of a negative control in every sequencing run. The obtained reads from individual samples were mapped to a SARS-CoV-2 reference genome (GISIAD sequence ID: EPI_ISL_1942165) to generate the consensuses using Geneious software (Biomatter, New

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

SARS-CoV-2 antibody measurement

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

Additional data for analysis

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

For viral load comparison, we used previously reported data of SARS-CoV-2 infected cases detected in Vietnam during the early phase of the pandemic in Vietnam between March and April 2020.[5]

Data analysis

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

Ethics

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

RESULTS

The outbreak and initial investigations

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

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

Demographics and clinical features

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

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

Viral loads

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

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

Compared with peak viral loads of cases infected with old SARS-CoV-2 strains detected in Vietnam between March and April 2020, peak viral loads of breakthrough cases were significantly higher, median log10 viral load in copies per mL (range): 9.1 (range: 2.8–10.2) vs. 6.7 (1.9–9.5), equivalent to 251 times higher for median viral loads. The differences were more profound among symptomatic cases while there was no difference in viral loads among asymptomatic cases between the two groups (Figure 2B).

Whole genome sequencing

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

Antibody development and case-control analyses

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

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

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

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

DISCUSSION

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

regarding the vaccine effectiveness in protecting against severe disease.[13-15] However, we found strong evidence demonstrating for the first time that fully vaccinated healthcare workers could still pass the virus between each other.

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

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

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

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

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

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

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REFERENCES

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

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

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

LEGENDS TO TABLES AND FIGURES

Table 1: Demographics and clinical characteristics of the study participants

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 presymtomatic 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 the cases and controls: median $\log_{10}$ viral load in 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 (1.9–8.6), $p=0.511$.

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 antibodes at both week 2 after the second doses (8 weeks after the first dose) abd at diagnosis were available and the uninfected controls, B) between the 62 case 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[#], n (%)	17 (27.4)	9 (27.3)	8 (27.6)
COVID-19 vaccination[¥], 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 (%)[$]	5 (8.1)	1 (3.0)	4 (13.8)
Pneumonia, n (%)**	3 (4.8)	0	3 (10.3)

Notes to Table 1:
*Symptomatic cases only
[¥]All receiving AstraZeneca vaccine; The second doses were given in last 2 weeks of April 2021.
[#]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).
[$]Chills (n=2), sweating (n=1), giddiness (n=1), red eyes (n=1), and diarrhea (n=1)
**One requiring oxygen supplementation via cannula route for 3 days.

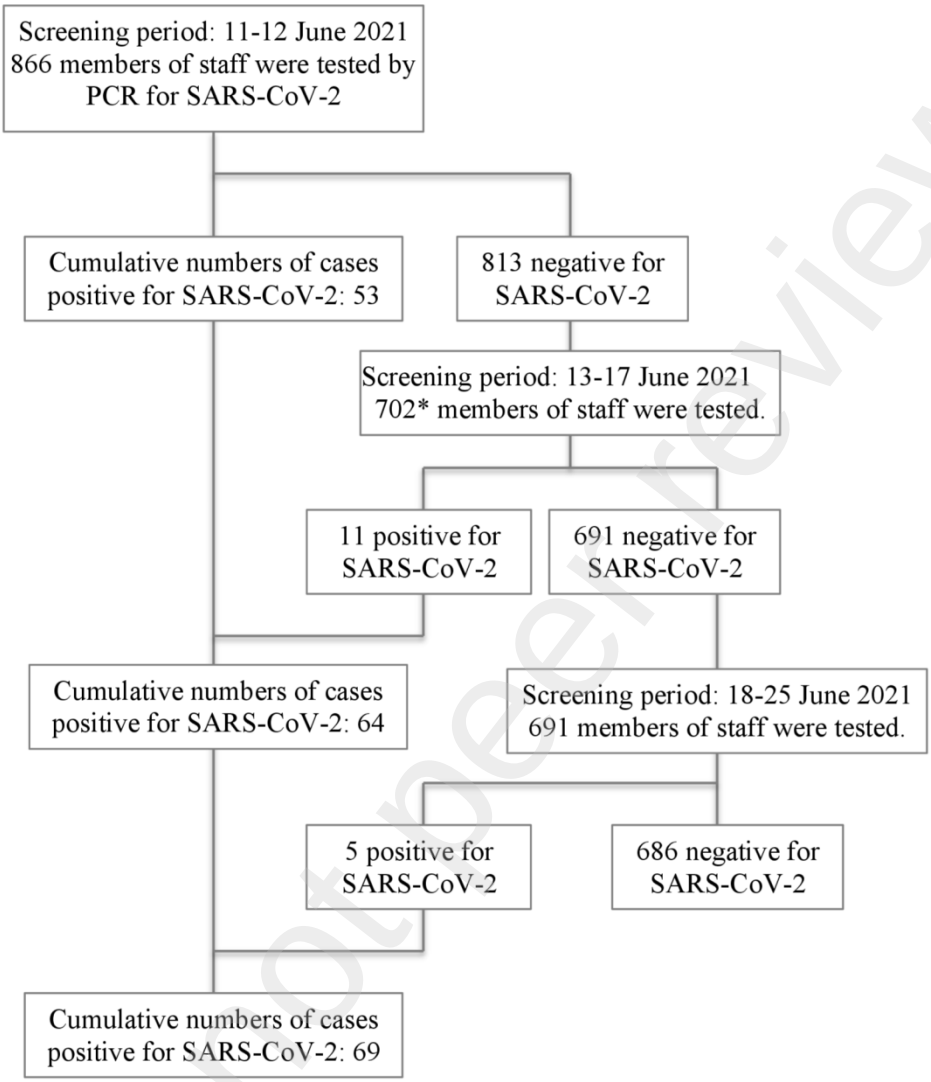


Figure 1: Flowchart showing timelines and results of SARS-CoV-2 RT-PCR screening before and during the lockdown (11-25 June 2021)

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

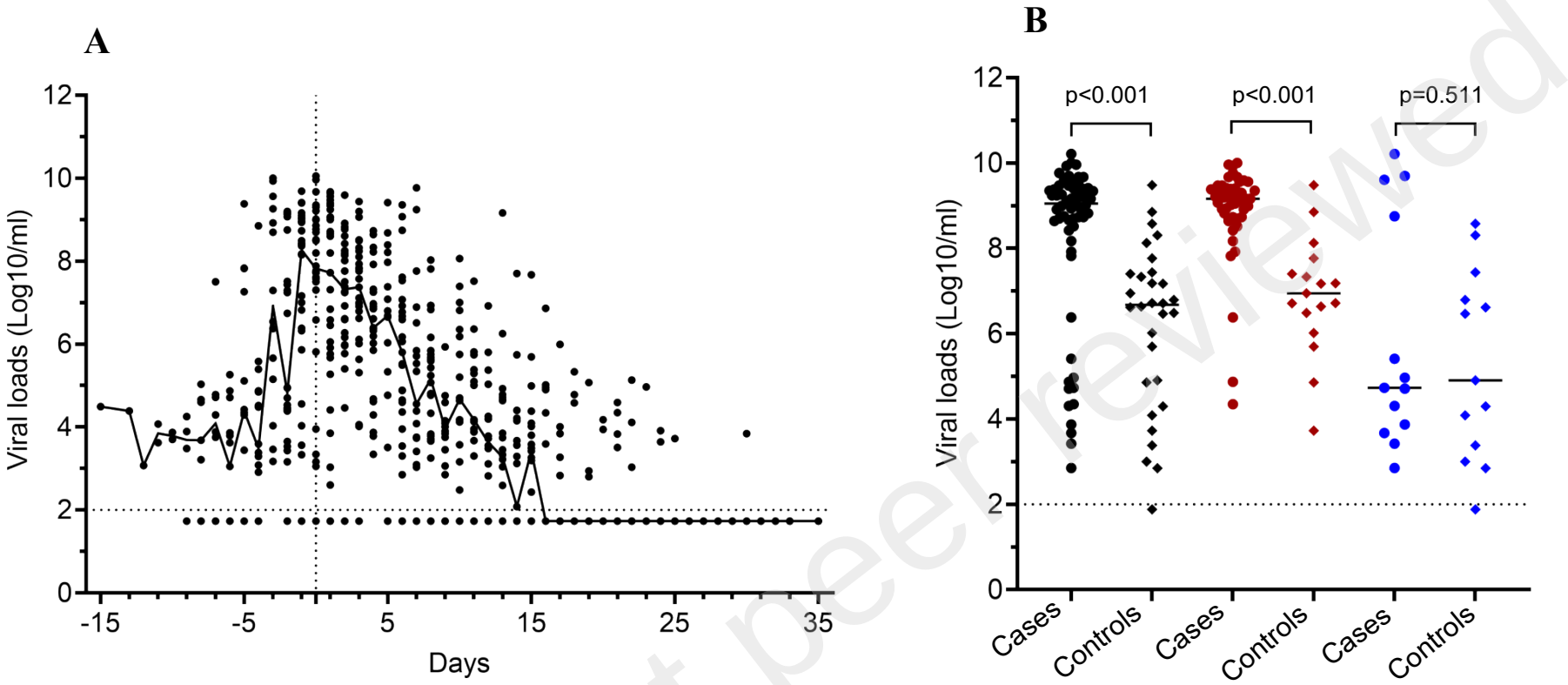


Figure 2: Viral load analyses, A) plot outlining kinetics of viral loads in relation to illness onset of the 49 study participants who were either symptomatic or presymtomatic at admission, B) comparison between peak viral loads of breakthrough infections (cases) and those (controls) infected with old 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

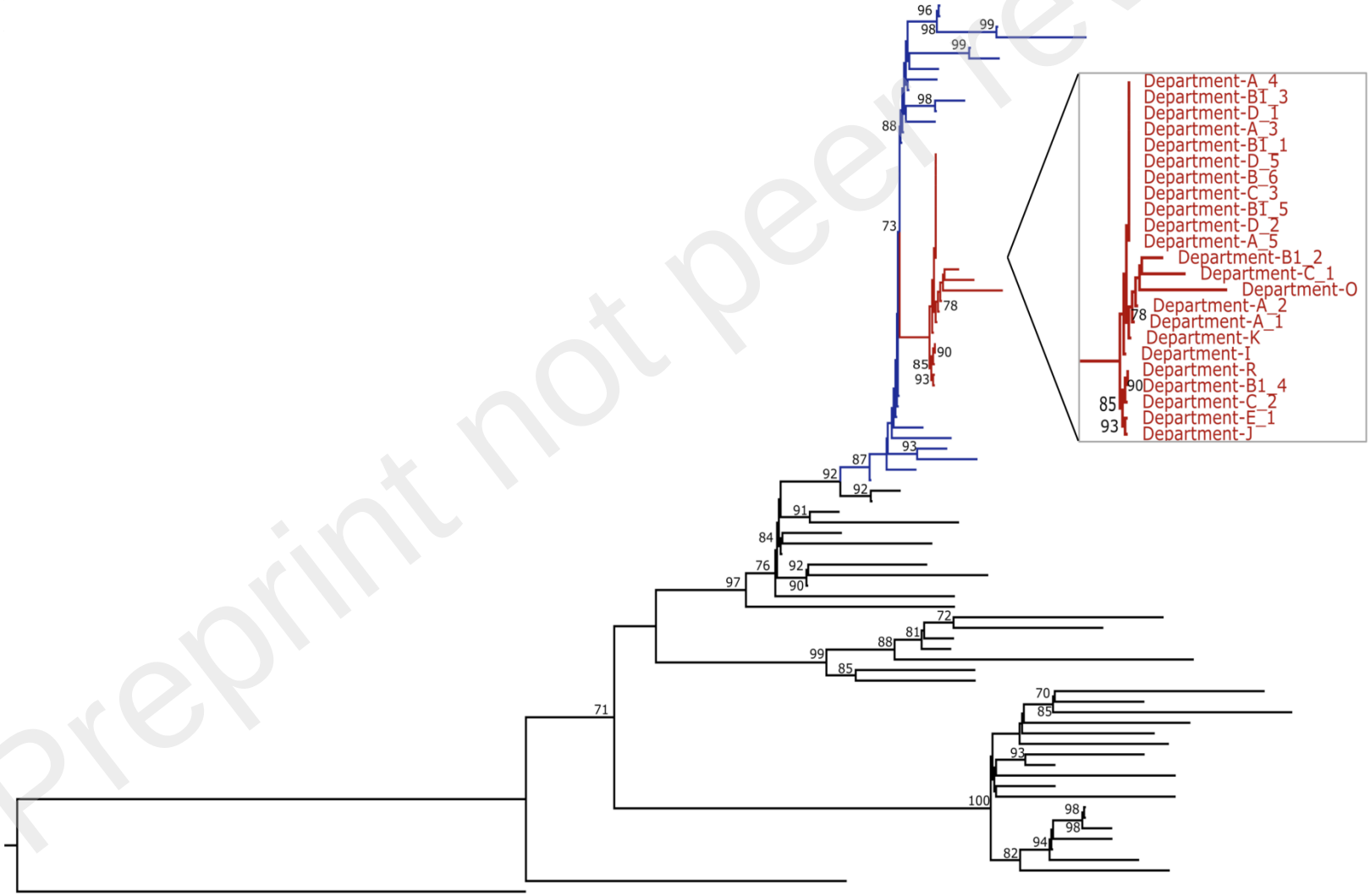


Figure 3: Maximum likelihood tree illustrating the relatedness between SARS-CoV-2 Delta variant strains obtained from cases of vaccine breakthrough infection (red) and contemporary Delta variant sequences obtained from cases of community transmission in Ho Chi Minh City (blue) and other provinces in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

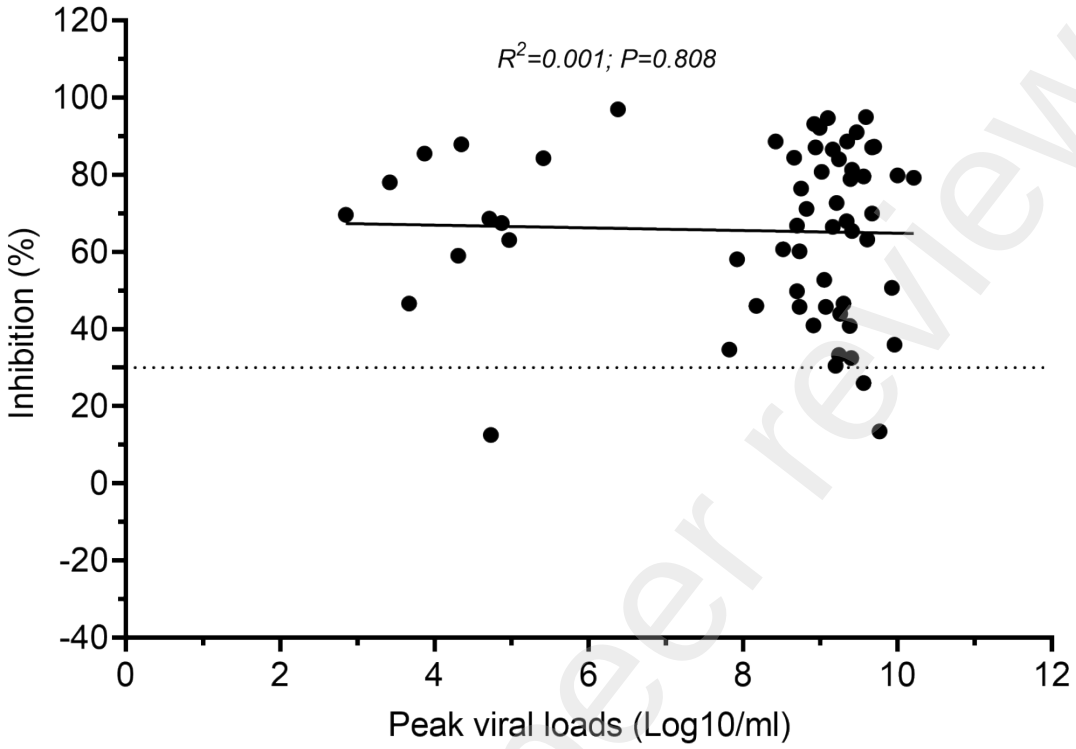


Figure 4: Correlation between neutralizing antibodies at diagnosis and peak viral loads during the course of infection

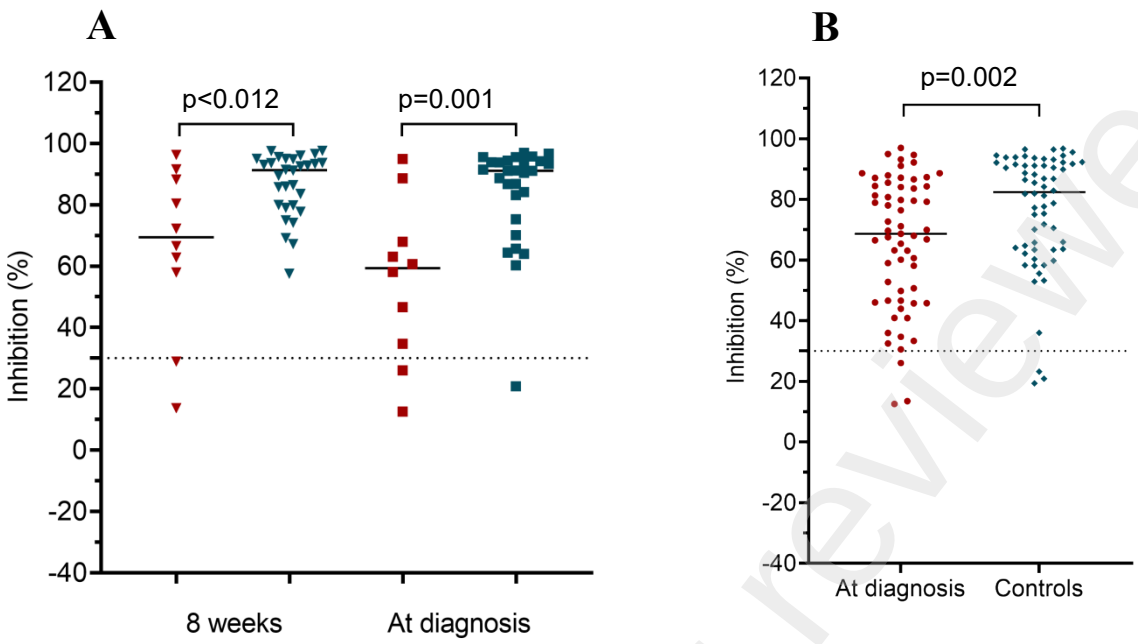
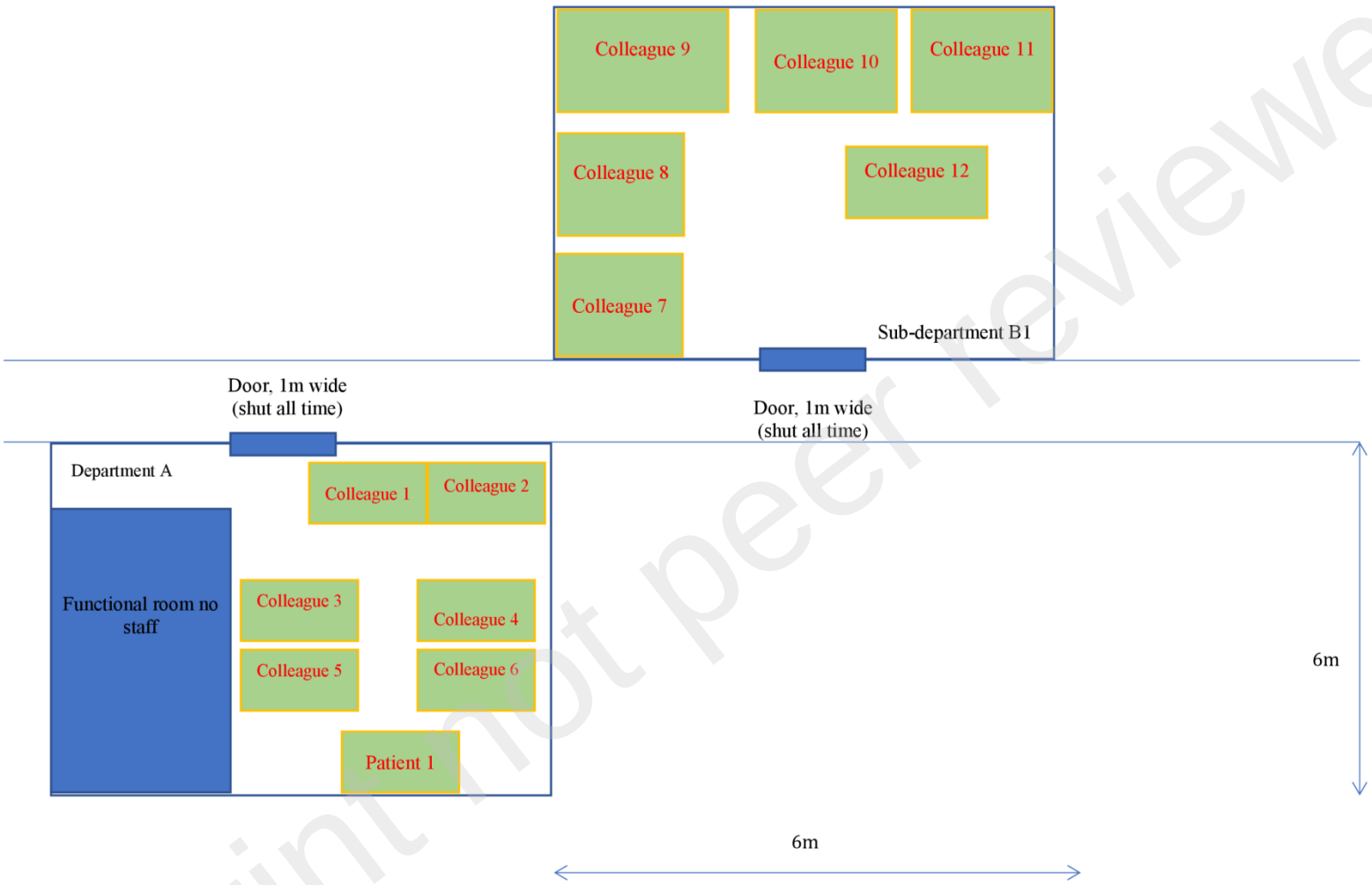


Figure 5: Comparison between neutralizing antibody levels of case patients (red) and uninfected controls (grey green). A) between the 10 case patients whose data on neutralizing antibodes at both week 2 after the second doses (8 weeks after the first dose) abd at diagnosis were available and the uninfected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

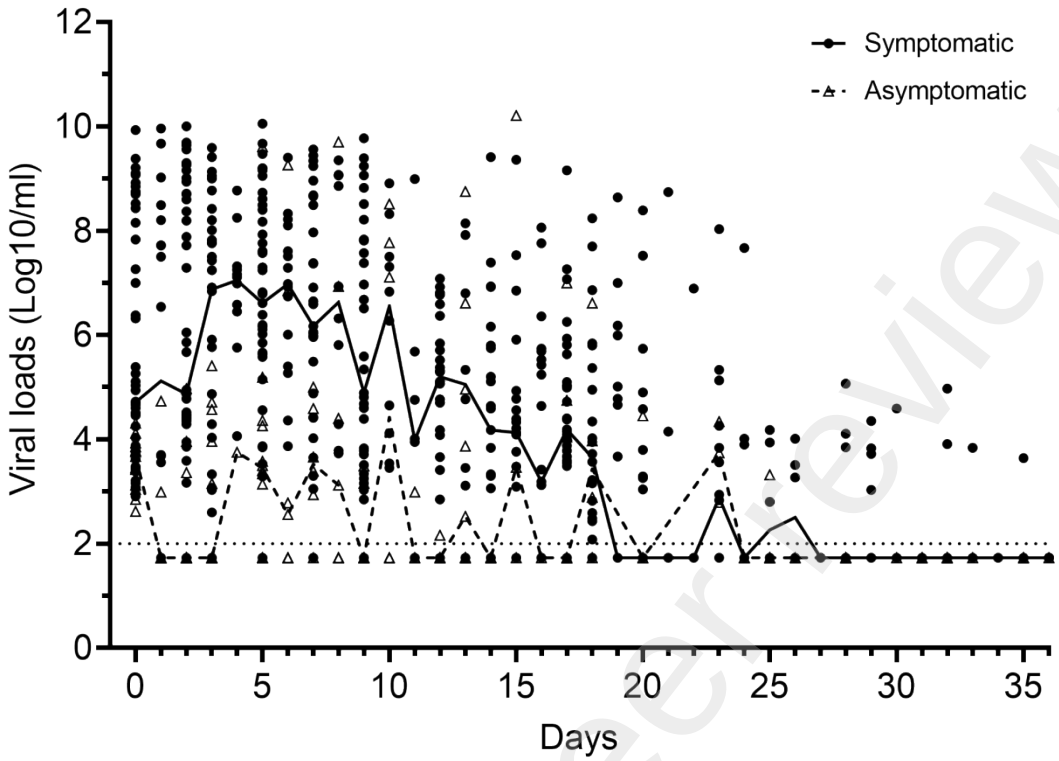
SUPPLEMENTARY MATERIALS

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

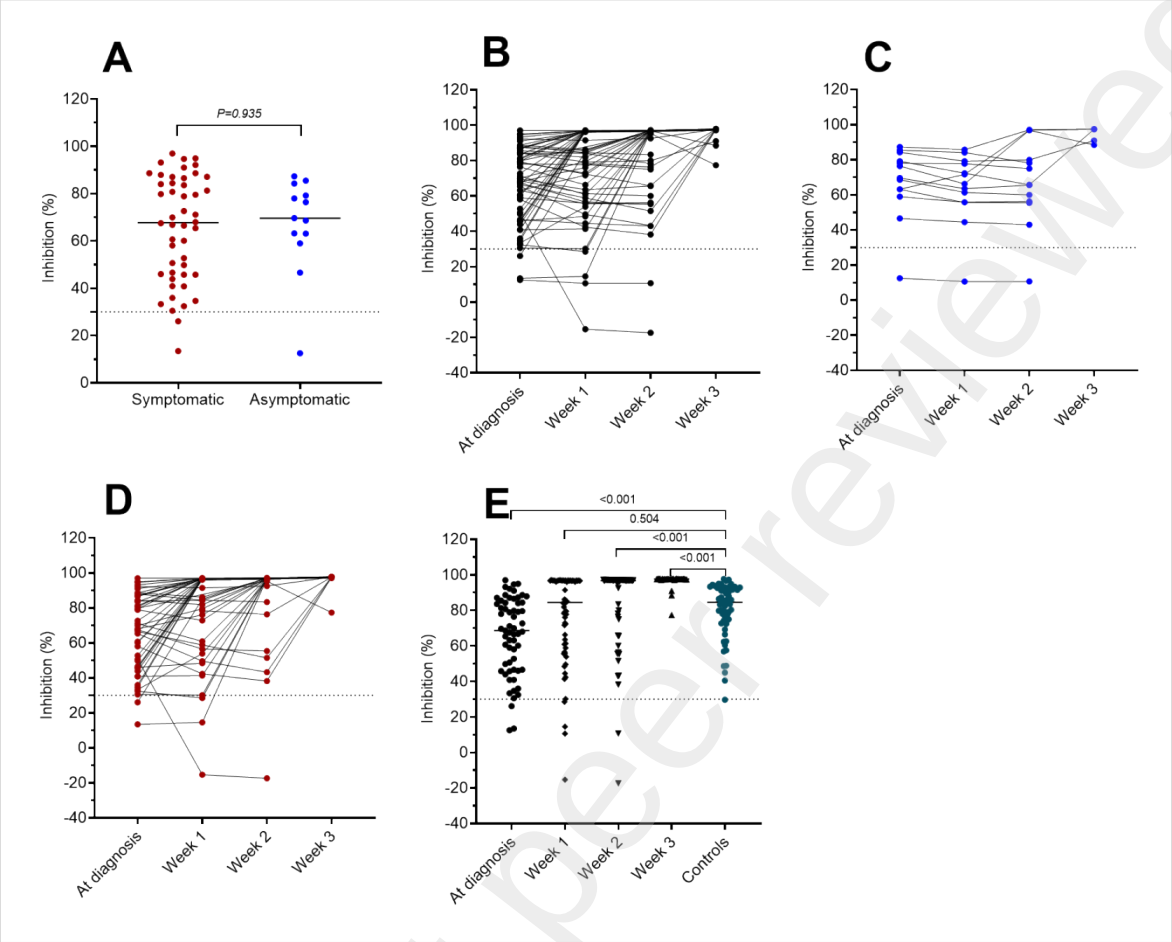


Supplementary Figure 1: Layout of office of patient 1 and a close office where 7/8 members were tested positive on 11th-12th June 2021. Office names are linked with Supplementary Table 1. Offices are equipped with air conditioners without mechanical ventilation. During working hours, doors are kept closed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



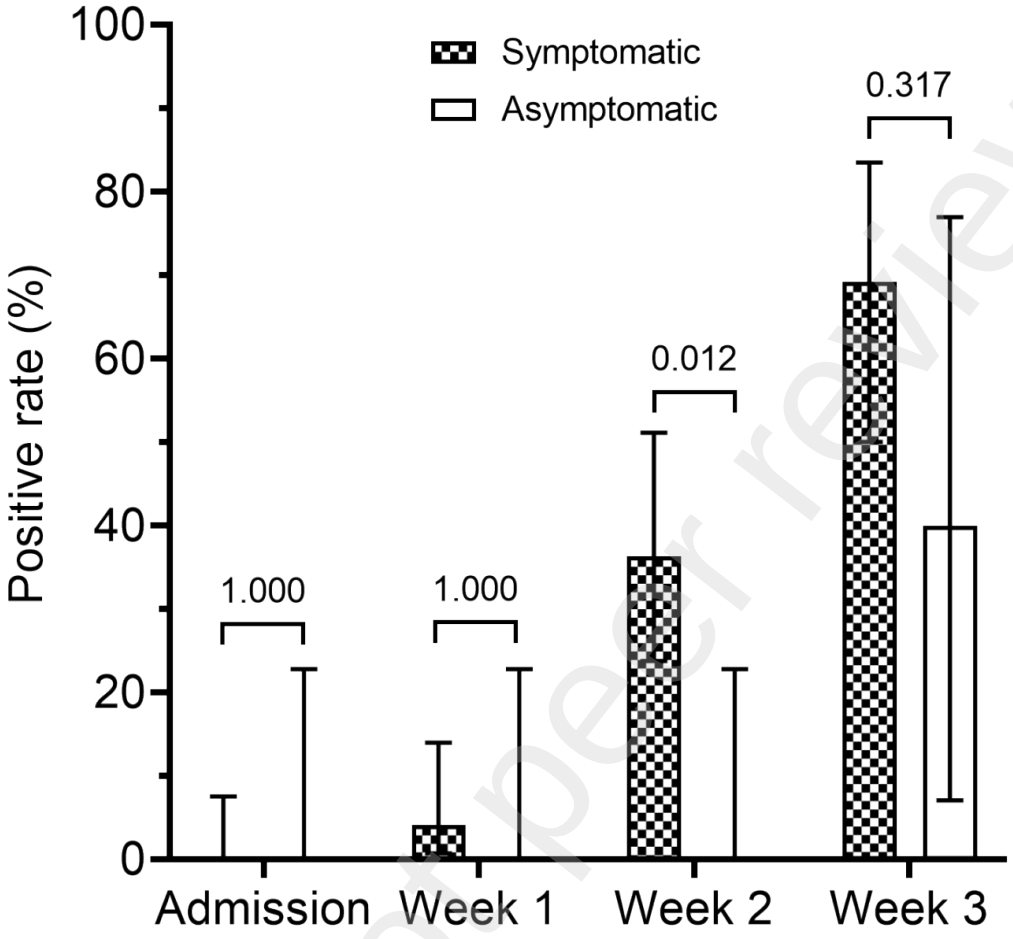
Supplementary Figure 2: Plot outlining kinetics of viral loads since PCR diagnosis during the course of hospitalization of the asymptomatic and symptomatic cases

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 symtomatic case who became seronegative at week 1 and week 2. Age and gender comparison between cases and controls: median in years (ragne): 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: Seroconverion rates against N protein at admission, and week 1, 2 and 3 after admission.

Note to Supplementary Figure 4: For the whole group, the seroconverstion 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.