

CLINICAL MEDICINE

Special Section: SARS-CoV-2

COVID-19 reinfection in the presence of neutralizing antibodies

Ju Zhang^{1,2,†}, Nan Ding^{1,2,†}, Lili Ren^{3,4,†}, Rui Song^{1,†}, Danying Chen^{1,2,†}, Xuesen Zhao^{1,2}, Budong Chen¹, Junyan Han^{1,2}, Jiarui Li^{1,2}, Yangzi Song^{1,2}, Lin Di⁵, Kai Han^{1,2}, Fengting Yu¹, Ruming Xie¹, Zhihai Chen¹, Wen Xie¹, Jingyuan Liu¹, Shan Cen⁶, Yuhai Bi^{7,8}, Angela R. Wu^{9,*}, Fujie Zhang^{1,*}, Chen Chen^{1,2,*} and Hui Zeng^{1,2,*}

Due to the high transmissibility of the SARS-CoV-2 virus, it continues to infect over 300 000 people worldwide per day (WHO statistics, December 2020), even almost one year after the first COVID-19 cases were confirmed [1,2]. One of the most important public health discussions being undertaken currently concerns the protective nature of the immune response and the possibility of reinfection in recovered individuals. Since seroconversion of SARS-CoV-2 antibodies has been detected in convalescent COVID-19 patients [3], many governments and public health agencies have proposed the idea of an ‘immunity passport’ to help with recovery of community social and economic norms; recovered individuals or those with detectable levels of antibodies against SARS-CoV-2, issued with an immunity passport, could be less stringent with lockdown, social distancing or travel rules, which would enable these individuals to travel or return to work [4,5].

However, a number of clinical studies have also revealed low titers of antibodies or rapid waning of antibodies against SARS-CoV-2 in convalescent patients [3,6], and raised concerns regarding the risks of SARS-CoV-2 reinfection. There have been anecdotal cases independently reported by several groups of patients testing positive for

SARS-CoV-2 virus again after recovery, which appears to be a recurrence of the infection [7,8]; several case studies of reinfection with a second bout of SARS-CoV-2 have also been identified in several countries [9–13]. However, more evidence is needed to distinguish *bona fide* reinfection of live replicating virus from both false positive polymerase chain reaction (PCR) results due to residual viral RNA, as well as from a recurrence of primary infection.

In our study of 273 patients, we report six cases of reinfection that all had negative PCR test results between the positive PCR tests during the two infection periods. In five of the six patients, viral genome sequencing results show unambiguous infection of a distinct viral strain in the second episode that was not in wide circulation prior to the time of secondary infection, ruling out the possibility of a relapse from primary infection. Of note, reinfection could occur shortly after recovery from primary infection. In addition, some of these patients mounted immune responses within the range that would be considered protective based on prior studies, yet were reinfected. These findings have strong and important implications for public health policy decisions, as well as in guiding efficacy assessment and development of vaccines.

SIX COVID-19 REINFECTION CASES CONFIRMED BY NUCLEIC ACID TESTS AND VIRAL GENOME SEQUENCING

From 29 January to 30 April 2020, Beijing Ditan Hospital admitted 273 cases of COVID-19, including 152 community-linked cases who were diagnosed from 20 January to 9 March 2020, and 121 international-linked cases (101 from Europe and 15 from North America; details in Supplementary Methods and Results 1.1) who were diagnosed from 29 February to 17 April 2020. The viral genome from the two periods displayed a distinct pattern [14]. We monitored the clinical and laboratory data during hospitalization and followed up these patients after they were discharged, when they met the recovery criteria according to the National Health Commission of the People’s Republic of China guidelines (no fever ≥ 2 days; obvious improvement of respiratory symptoms and pulmonary images; twice consecutive negative Real-time polymerase chain reaction (RT-PCR)) [15]. From 1 March, we found 28 patients who had twice consecutive positive tests for SARS-CoV-2 during follow-up among these patients.

To determine which of these were true reinfections, we used the MINERVA sequencing strategy [16] on paired

clinical specimens obtained in two episodes of these 28 patients. We ultimately obtained paired complete viral genomes from seven patients. Phylogenomic analysis on these complete viral genomes showed one of the paired-genomes was from the same lineage, while the other six paired-genomes were attributed to different lineages or descending lineages with 3–11 distinct single nucleotide polymorphisms (SNPs) between each pair (Table 1 and Table S1). A different viral lineage between the first and second infection episodes, particularly with the negative PCR results between episodes (Table S2), is strong evidence of true reinfection rather than false positive or relapse of the primary infection. More importantly, five of these six pairs sampled in the second episode were found to be D614G mutants (Table 1). This variant was almost completely absent in China prior to March [14], and was identified as the predominant variant in Europe, gradually becoming frequent worldwide toward the end of March [17]. Furthermore, each of the viral genomes sequenced contained a different set of SNPs at various positions (Table 1), which made it extremely unlikely that these were the result of cross contamination between patient samples; if a single or a few samples contaminated others, the SNPs observed would be the same across samples which was not the case here. To further validate sample identity, we additionally performed host mitochondrial DNA analysis to rule out the possibility of sample mix-ups (Fig. S1, Supplementary Methods and Results 1.3). Taken together, these data provide robust molecular evidence for reinfection from *bona fide* replicating virus in at least six patients.

EPIDEMIOLOGICAL AND CLINICAL DATA OF PATIENTS WITH REINFECTION

Next, we assessed the clinical and epidemiological data of these six patients. As summarized in Table S2, they comprised five adults (age: 33–84 years) and one 2-year-old child. Two were

critical COVID-19 patients (P1, P6), and the other four were moderate cases (P2–P5) in their primary infections. None of them had autoimmune diseases, cancer or a history of immunosuppressive drug use. The interval between the end of the primary infection and the beginning of the reinfection ranged from 19 to 57 days (Fig. 1a, Table S2). All patients had at least two negative viral RNA tests during the recovered phase between infection periods; two of them (P1 and P2) had 12 and five negative viral RNA tests respectively during this recovered phase (Fig. 1a, Table S2). During the secondary infection, five cases (P1–P4, P6) tested positive for SARS-CoV-2 viral RNA 3–14 times, and four patients (P1–P3, P6) had low cycle threshold (Ct) values, ranging from 24 to 28, representing high viral loads. Viral RNA positive durations lasted at least nine days in five cases (P1–P4, P6; Fig. 1a, Table S2). No difference in the infection duration and the viral loads of the SARS-CoV-2 RNA was observed between the primary infections and secondary infections (Table S2). Three cases (P1–P3) developed symptoms again after the first negative intervals, including fever, cough, expectoration and stuffy nose (Fig. 1a, Table S2). Meanwhile, CT scan of P1 and P2 exhibited new infected lesions, including patchy ground-glass opacity and consolidation in the chest (Figs 1b and S2). These clinical data further support the notion that these patients were reinfected with new viruses rather than re-testing positive for the same primary infection.

We also performed contact-tracing to assess potential sources of reinfection. Among these patients, case P1 stayed in the intensive care unit due to concomitant cardiorenal complications after prior negative COVID-19 test. She had a history of sharing the ward with other COVID-19 patients, and tested positive for viral RNA again during hospitalization. The other five cases (P2–P6) re-tested positive during the follow-up after discharge. Case P5 had a contact history with a confirmed COVID-19 patient with an identical viral genome except for one SNP difference before his second episode

(Table S1). Case P2 revisited the hospital after developing COVID-19 symptoms. The other three patients (P3, P4 and P6) were self-quarantined for 14 days according to the Diagnosis and Treatment Protocol for COVID-19, and revisited the hospital for follow-up and re-testing.

REINFECTION OCCURRED IN THE PRESENCE OF VARIED LEVELS OF NEUTRALIZING ANTIBODIES

We further assessed the dynamics of antibody response by measuring specific IgM/IgG targeting the receptor-binding domain (RBD) of S protein or N protein (Figs 1c and S3, Table S3). Various antibody levels were observed in convalescent serum/plasma in these six patients. P2 and P4 had low anti-RBD IgM/IgG ($\leq 1:40$) responses to the primary infection. In the other three patients (P1, P3 and P6), titers reached 1:80–1:320 for RBD-IgM and IgG (Fig. 1c, Table S3). During the secondary infection, cases P1 and P2 displayed secondary immune responses with an increase in serum antibody titers: for example, case P1 RBD-IgM increased from 1:10 to 1:2560, NP-IgM from 1:20 to 1:80, and NP-IgG from 1:640 to 1:2560 (Figs 1c and S3, Table S3).

Since five of the six cases (P1–P5) were infected with the D614G variants in the secondary infection (Table 1), we also performed microneutralization assays with live virus of both reference SARS-CoV-2 and D614 variants in parallel. Consistent with ELISA data, the samples from case P2 and P4 exhibited low inhibitory dilution 50 (ID₅₀) during the primary and secondary infections; whereas the samples from case P1 and P3 had a certain amount of neutralizing activity against both reference SARS-CoV-2 and D614 variants (Fig. 1c, Table S3). Of note, the neutralizing titers against live virus with D614G mutation were 1:18.6 (P1) and $>1:64$ (P3), respectively (Fig. 1c, Table S3). We compared these data with the previous study on 454 convalescent samples from 178 COVID-19 confirmed patients with the identical microneutralization system [18] (neutralizing titer:

Table 1. SNPs on the viral genomes sequenced from the six reinfected patients.

SNP	Position	Gene	Class	Amino Acid substitution	Sample											
					P1.1	P1.2	P2.1	P2.2	P3.1	P3.2	P4.1	P4.2	P5.1	P5.2	P6.1	P6.2
C8782T	8782	<i>ORF1ab</i>	Synonymous variant	p.2839S	C	C	C	C	C	C	C	C	C	C	T	C
T28144C	28 144	<i>ORF8</i>	Missense variant	p.84L > S	T	T	T	T	T	T	T	T	T	T	C	T
C241T	241	<i>5'UTR</i>	Upstream gene variant	-	C	T	C	T	C	T	C	T	C	T	C	C
C14408T	14 408	<i>ORF1ab</i>	Missense variant	p.4715P > L	C	T*	C	T	C	T	C	T*	C	T	C	C
A23403G	23 403	<i>S</i>	Missense variant	p.614D > G	A	G	A	G	A	G	A	G*	A	G	A	A
C3037T	3037	<i>ORF1ab</i>	Synonymous variant	p.924F	C	N	C	T	C	T	C	T	C	T	C	C
G26144T	26 144	<i>ORF3a</i>	Missense variant	p.251G > V	T	G	G	G	T	G	G	G	G	G	G	G
G3231T	3231	<i>ORF1ab</i>	Missense variant	p.989G > V	G	T	G	G	G	G	G	G	G	G	G	G
T16254C	16 254	<i>ORF1ab</i>	Synonymous variant	p.5330V	T	C	T	T	T	C	T	T	T	T	T	T
T16545C	16 545	<i>ORF1ab</i>	Synonymous variant	p.5427V	T	C	T	T	T	T	T	T	T	T	T	T
A26449T	26 449	<i>E</i>	Stop gained	p.69R> ^a	A	T	A	A	A	A	A	A	A	A	A	A
C313T	313	<i>ORF1ab</i>	Synonymous variant	p.16L	C	C	C	T	C	C	C	C	C	C	C	C
T14950C	14 950	<i>ORF1ab</i>	Missense variant	p.4896F > L	T	T	T	C	T	T	T	T	T	T	T	T
G28881A	28 881	<i>N</i>	Missense variant	p.203R > K	G	N	G	A	G	G	G	G	G	G	G	G
G28882A	28 882	<i>N</i>	Synonymous variant	p.203R	G	N	G	A	G	G	G	G	G	G	G	G
G28883C	28 883	<i>N</i>	Missense variant	p.204G > R	G	N	G	C	G	G	G	G	G	G	G	G
G13617T	13 617	<i>ORF1ab</i>	Missense variant	p.4451K > N	G	G	G	G	T	G	G	G	G	G	G	G
C337T	337	<i>ORF1ab</i>	Synonymous variant	p.24R	C	C	C	C	C	C	T	C	C	C	C	C
C3429T	3429	<i>ORF1ab</i>	Missense variant	p.1055T > I	C	N	C	C	C	C	T	C	C	C	C	C
C6268T	6268	<i>ORF1ab</i>	Synonymous variant	p.2001A	C	C	C	C	C	C	T	C	C	C	C	C
C18512T	18 512	<i>ORF1ab</i>	Missense variant	p.6083P > L	C	C	C	C	C	C	T	C	C	C	C	C
G237T	237	<i>5'UTR</i>	Upstream gene variant	-	G	G	G	G	G	G	G	T	G	G	G	G
G2229A	2229	<i>ORF1ab</i>	Missense variant	p.655C > Y	G	G	G	G	G	G	G	A	G	G	G	G
T19561A	19 561	<i>ORF1ab</i>	Missense variant	p.6433L > M	T	T	T	T	T	T	T	A	T	T	T	T
T4008C	4008	<i>ORF1ab</i>	Missense variant	p.1248F > S	T	T	T	T	T	T	T	T	C	T	T	T
T28031C	28 031	<i>ORF8</i>	Synonymous variant	p.46Y	T	T	T	T	T	T	T	T	C	T	T	T
C1059T	1059	<i>ORF1ab</i>	Missense variant	p.265T > I	C	C	C	C	C	C	C	N	C	T	C	C
G25217T	25 217	<i>S</i>	Missense variant	p.1219G > C	G	G	G	G	G	G	G	G	G	T	G	G
G25563T	25 563	<i>ORF3a</i>	Missense variant	p.57Q> H	G	G	G	G	G	G	G	G	G	T	G	G
C27389T	27 389	<i>Intergenic</i>	Downstream gene variant	-	C	C	C	C	C	C	C	C	C	C	C	T

^aShows the SNPs validated by PCR-Sanger sequencing approach, which were not covered by enough reads after removing duplicates. N = A or C or G or T. Nucleotides in bold text indicate SNPs.

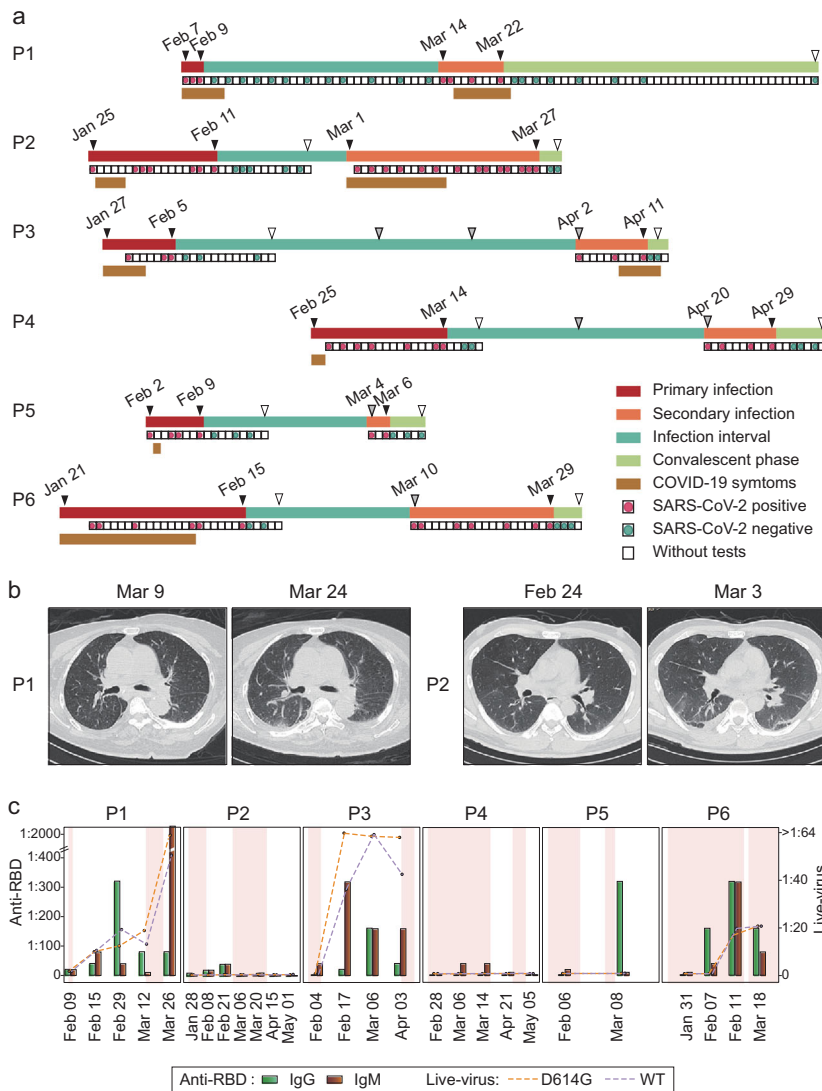


Figure 1. Detailed timelines and high-resolution chest CT scans of reinfected cases. (a) Timeline of the six reinfected COVID-19 patients. Infection stages are highlighted in different colors on the first line for each case. RT-PCR results and duration of hospitalization are shown in the second lines for each patient. Durations of COVID-19 symptoms are shown in the third lines. Red line, primary infection; orange line, secondary infection; green line, infection interval between two infection episodes; light green line, convalescent phase of the secondary infection; red dot, positive RT-PCR tests; green dot, negative RT-PCR test; tan line, symptom duration; gray arrows, follow-up dates initiated by doctors or patients; white arrows, discharge dates from hospital. (b) Representative high-resolution CT images before and after the secondary infections. Increasing and multifocal ground-glass changes in subpleural areas were observed (P1: dorsal segment of right lower lobe; P2: right upper lobe, left lingual lobe and bilateral lower lobes). (c) Titer dynamics of antibodies against SARS-CoV-2 RBD, and neutralizing activity against live virus of reference SARS-CoV-2 and D614G variants in six patients. Green bars, anti-RBD IgG titers; sienna bars, anti-RBD IgM titers; line and dots, neutralizing ID50 against authentic virus of SARS-CoV-2 reference strain (purple) and D614G variant (orange). Background color shows the infection period, with the first and second infection periods shaded, and recovered periods in white.

median, 1 : 19; qualitative reading inventory (QRI), 1 : 10–1 : 28.2; Fig. S4), and the ID50 of case P1 and P3 exceeded 44.3% and 97.4%

of ID50 values of samples from COVID-19 patients, respectively (detail in the Supplementary Methods and Results 1.8).

Generally, the antibody titer and neutralization ability were in agreement for all reinfection cases (Fig. 1c), consistent with the literature [18,19]. In prior SARS-CoV-2 studies, recovered patients with antibody titers above 1 : 160 could maintain stable serum antibody levels for up to 148 days [18,19]. We observed that three patients with initially higher antibody titers after recovery (P1, P3, P6) were able to maintain these levels well into the secondary infection (Fig. 1c). Furthermore, we observed the neutralizing titers against both SARS-CoV-2 reference strain and D614G variants increased drastically in sera/plasma of case P1 after secondary infection, suggesting that the immune memory response was activated after secondary challenge (Figs 1c and S3, Table S3). But in all of these cases, P1, P3 and P6, reinfection occurred nonetheless, suggesting that potential COVID-19 reinfections could still occur even in individuals with measurable levels of neutralizing antibodies.

DISCUSSION

Reinfection has been observed in seasonal beta-coronavirus, such as HKU1 and OC4316 [20]; recently single cases of SARS-CoV-2 reinfection were also reported in Hong Kong, China [9]; the United States [10]; Ecuador [11]; Belgium [12] and the Netherlands [13]. Herein, we identified six cases of reinfection. Importantly, the time interval between the two bouts of infection in the present study ranged from 19 to 57 days (Fig. 1a, Table S2), indicating that reinfection could occur much earlier than previously suspected.

The D614G haplotype was almost non-existent in China during the time of the primary infection, but was found as the variant in five of the six reinfections (Table 1). Given the timing of the introduction of this haplotype to China, there is overall compelling evidence proving that the viral variants in the secondary infection are different from that of the first, and that the main variants (D614G) found in the second infections are highly unlikely to have been involved in the first infections. In addition to viral

phylogenetic data, the RT-PCR assays performed by a laboratory outside the hospital, as well as the clinical findings during the second episode, collectively strengthen the assumption that these are *bona fide* SARS-CoV-2 reinfections: during the secondary infection (i) patients tested positive for SARS-CoV-2 RNA for 3–26 days; (ii) the lowest Ct value of the SARS-CoV-2 RNA for each patient was 24–37 during this period; (iii) COVID-19-related symptoms reappeared accompanied by new pulmonary inflammatory lesions; (iv) microneutralization assays revealed secondary humoral immune responses (Fig. 1, Table S2). Together, this is compelling evidence of the second episode being caused by a new virus, rather than a persistence of the virus causing the first episode.

Whether reinfection would occur in an individual is not only determined by the magnitude and duration of that individual's specific immunity, but also the varied circumstances of their exposure risk to the virus. The conventional wisdom is that immunity would protect the recovered patients for a long period, and the possibility of reinfection was not considered or taken seriously. Of note, despite strict public health policies and social distancing measurements in Beijing, we still identified multiple cases of SARS-CoV-2 reinfection by monitoring 'recovered' patients, suggesting that reinfection might not be a rare event as many previously thought. However, it is not feasible to speculate or derive the population rate or risk of reinfection based on these data. Considering the escalation of the pandemic in many countries around the world, as well as the continued insufficiency of diagnostic resources in many communities, the risk of re-exposure to SARS-CoV-2 is still high, and reinfection certainly is a cause for alarm or concern.

It has been proposed that reinfection is a result of inadequate humoral protection against SARS-CoV-2. Consistent with this notion, in the Hong Kong reinfection case the patient did not have adequate amounts of virus-specific antibodies [9]. This is also the case for some patients in this study. However, a recent

study revealed that robust neutralizing antibodies to SARS-CoV-2 infection remain relatively stable for several months after infection [19,21]. Concordant with their findings, we also note substantial titers of neutralizing antibodies before the secondary infection in several patients in this study (Fig. 1c, Table S3). This is further evidence that post-convalescence patients with neutralizing antibodies should not be considered safe against a second bout of infection.

Substantial work has been done to investigate the possible changes in SARS-CoV-2 infectivity and immune evasion, and so far, there is little evidence to suggest viral evolution that trends toward increasing viral ability to reinfect or evade antibodies [22]. In this study, the viral genomes sequenced from the secondary infections are found to be of a distinct lineage from that of the primary infection (Table S1), as confirmed by phylogenetic classification algorithms [23], and genetic differences between samples were found with high confidence. Further comparisons of complete viral genomes between primary and secondary infections in each paired sample revealed 3–11 SNPs (Table 1), but interestingly, none of the genomic differences were in the RBD region. In addition, although five viral genomes from the second infection contained a common mutation D614G in the S protein (Table 1), serum from these patients was still able to neutralize D614G viral variants *in vitro* (Fig. 1c, Table S3) [22], negating the possibility that these mutations afford the virus immune escape capabilities.

Clearly, there remains much unknown about COVID-19, and characterizing the underlying mechanism of reinfection could help to inspire development of new vaccines that are safer, more effective and more protective. That SARS-CoV-2 can cause a second infection in the presence of measurable antibody responses calls into question whether a threshold level of antibody response is required for protection. Vaccine development will need to consider not just whether a response is raised, but also the quantitative level of antibody response raised as an important endpoint for testing and trials. Furthermore,

vaccine-induced immunity might be different from natural immunity; vaccines may not induce the same T cell responses as a true SARS-CoV-2 infection does [24]. Studies have accumulated evidence of more broadly dysregulated immune function during viral infection [25], and consistently, we also observed decreased CD4⁺ T cell counts in five adult cases, and decreased CD8⁺ T cell counts in two critical COVID-19 patients (Tables S4 and S5). Therefore, an effective vaccine may also need to mount T cell immunity, and development of vaccines that elicit both neutralizing antibodies and T-cell responses, which may be achievable by using a combination of different vaccine types and approaches, should be encouraged [26].

Summarily, we demonstrated that COVID-19 reinfections could occur during the convalescent stage, even in cases with natural-infection-induced humoral immunity. Several cases also developed characteristic COVID-19 symptoms. Both investigation of unique patient cohorts such as those in this study, as well as reasonable and responsible discussions about the results, have important implications for public health. Specifically, to effectively counter the pandemic and aid individual patient recovery, we need both effective and protective vaccines in addition to policies that promote personal protective behaviors for as long as necessary. Inappropriate public health measures could result in recurring waves of COVID-19, thus, public health policies, vaccine development and assessment strategies should be carefully evaluated in light of this study's findings.

SUPPLEMENTARY DATA

Supplementary data are available at [NSR](#) online.

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AUTHOR CONTRIBUTIONS

J.Z., N.D. and L.R. contributed to conceptualization, data collection, data analysis, results interpretation and manuscript writing. H.Z., F.Z. and A.W. contributed to conceptualization, results interpretation and manuscript writing. C.C. and R.S. contributed to data analysis and manuscript writing. D.C., X.Z., B.C., J.H., J.L., Y.S., L.D., K.H., F.Y., R.X., Z.C., W.X., J.L., S.C. and Y.B. contributed to data collection and results interpretation.

Conflict of interest statement. None declared.

Ju Zhang^{1,2,†}, Nan Ding^{1,2,†}, Lili Ren^{3,4,†}, Rui Song^{1,†}, Danying Chen^{1,2,†}, Xuesen Zhao^{1,2}, Budong Chen¹, Junyan Han^{1,2}, Jiarui Li^{1,2}, Yangzi Song^{1,2}, Lin Di⁵, Kai Han^{1,2}, Fengting Yu¹, Ruming Xie¹, Zhihai Chen¹, Wen Xie¹, Jingyuan Liu¹, Shan Cen⁶, Yuhai Bi^{7,8}, Angela R. Wu^{9,*}, Fujie Zhang^{1,*}, Chen Chen^{1,2,*} and Hui Zeng^{1,2,*}

¹Beijing Ditan Hospital, Capital Medical University, China; ²Beijing Key Laboratory of Emerging Infectious Diseases, China; ³NHC Key Laboratory of Systems Biology of Pathogens and Christophe Mérieux Laboratory, Institute of Pathogen Biology, Chinese Academy of Medical Sciences and Peking Union Medical College, China; ⁴Key Laboratory of Respiratory Disease Pathogenomics, Chinese Academy of Medical Sciences and Peking Union Medical College, China; ⁵Beijing Advanced Innovation Center for Genomics, Biomedical Pioneering Innovation Center, Peking University, China; ⁶Institute of Medicinal Biotechnology, Chinese Academy of Medical Sciences and Peking Union Medical School, China; ⁷CAS Key Laboratory

of Pathogenic Microbiology and Immunology, Institute of Microbiology, Center for Influenza Research and Early-Warning (CASIRE), CAS-TWAS Center of Excellence for Emerging Infectious Diseases (CEEID), Chinese Academy of Sciences, China; ⁸University of Chinese Academy of Sciences, China and ⁹Division of Life Science and Department of Chemical and Biological Engineering, Hong Kong University of Science and Technology, China

*Corresponding authors. E-mails: zenghui@ccmu.edu.cn; chenchen1@ccmu.edu.cn; treatment@chinaaids.cn; angelawu@ust.hk

†Equally contributed to this work.

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