Genomic, immunological, and clinical analysis of COVID-19 vaccine breakthrough infections in Beijing, China

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Abstract
As the coronavirus disease 2019 (COVID-19) pandemic is still ongoing and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants are circulating worldwide, an increasing number of breakthrough infections are being detected despite the good efficacy of COVID-19 vaccines. Data on 88 COVID-19 breakthrough cases (breakthrough infections group) and 41 unvaccinated cases (unvaccinated group) from June 1 to August 22, 2021, were extracted from a cloud database established at Beijing Ditan Hospital to evaluate the clinical, immunological, and genomic characteristics of COVID-19 breakthrough infections. Among these 129 COVID-19 cases, 33 whole genomes were successfully sequenced, of which 23 were Delta variants, including 15 from the breakthrough infections group. Asymptomatic and mild cases predominated in both groups, but two patients developed severe disease in the unvaccinated group. The median time of viral shedding in the breakthrough infections group was significantly lower than that in the unvaccinated group (p = 0.003). In the breakthrough infections group, the IgG titers showed a significantly increasing trend (p = 0.007), and the CD4+ T lymphocyte count was significantly elevated (p = 0.018). For people infected with the Delta variant in the two groups, no significant difference was observed in either the quantitative reverse-transcription polymerase chain reaction results or viral shedding time. In conclusion, among vaccinated patients, the cases of COVID-19 vaccine breakthrough infections were mainly asymptomatic and mild, IgG titers were significantly increased and rose rapidly, and the viral shedding time was shorter.

KEYWORDS
clinical outcome, COVID-19, Delta variant, immunological characterization, vaccine breakthrough infections, whole-genomic analysis
1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) has now become a significant public health concern worldwide. Globally, as of January 14, 2022, there have been 318,648,834 confirmed cases of COVID-19, including 5,518,343 deaths, reported to the World Health Organization (WHO). Thanks to a series of unprecedented strict public health measures and extremely large numbers of quantitative reverse-transcription polymerase chain reaction (RT-qPCR) tests for residents implemented by China, China had almost stopped large-scale domestic COVID-19 transmission, but occasional outbreaks associated with imported cases and cold-chain products contaminated with viruses were detected in some regions.

Vaccines have been developed and rapidly implemented to control the global spread of COVID-19, some of the vaccines have been authorized by the WHO for emergency use. The major types of vaccines in the current use in China are inactivated vaccines, adenovirus vector vaccines, and recombinant subunit vaccines, of which inactivated vaccines are the most widely used. The first mass vaccination program started in early December 2020. As of January 13, 2022, a total of 9,283,076,642 vaccine doses have been administered globally. COVID-19 vaccines effectively prevent serious illness, and death; however, a fraction of fully vaccinated people still develop SARS-CoV-2 infection. An infection that occurs in a fully vaccinated person is referred to as a “breakthrough infection.” In the context of widespread vaccine coverage, breakthrough infection has become a new challenge in fighting against COVID-19.

With the continuous transmission and mutation of SARS-CoV-2, the emergence of many kinds of variants such as variants of interest (VOIs) and variants of concern (VOCs) had posed an increased risk to global public health, especially in causing vaccine-breakthrough infections. Despite vaccines have played an essential role in reducing COVID-19 infections, particularly in reducing the incidence of severe cases and deaths, whether vaccination can reduce the viral load and shedding time of breakthrough infections has recently become the main topic. Many vaccine breakthrough infections have been reported worldwide; however, only a few studies related to breakthrough infections have been conducted in China. In the present study, we summarized the clinical data of patients with breakthrough infections at Beijing Ditan Hospital, the only hospital that receives COVID-19 patients in Beijing among the study period, compared them with the unvaccinated group, and further analyzed the viral genome sequences and clinical and immunological features.

2 | MATERIALS AND METHODS

2.1 | Ethical approval

This study was approved by the Institutional Review Board of Beijing Ditan Hospital, Capital Medical University in Beijing (approval number JDLY2020-020-01).

2.2 | Study design and recruitment of cases

In January 2020, we established a cloud database of COVID-19 patients at Beijing Ditan Hospital. In this study, we extracted a total of 129 adult COVID-19 cases from June to August 2021, and the cases were divided into the breakthrough infection group, which was vaccinated with different types of vaccines, and the unvaccinated group. COVID-19 patients were diagnosed based on the 8th version of the Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia Patients, and the clinical severity was categorized into 4 grades: mild (the clinical symptoms were mild, and there was no evidence of pneumonia on imaging), moderate (fever and respiratory symptoms, imaging manifestations of pneumonia), severe (dyspnea with a respiratory rate of more than 30/min, hypoxemia with oxygen saturation of less than 93%, and PaO₂/FiO₂ of less than 300 mmHg; clinical symptoms that had gradually worsened; and lung imaging showing that the lesions had progressed by more than 50% within 24–48 h), and critical (developed complications, including respiratory failure requiring mechanical ventilation, shock, or other organ failure requiring intensive care unit [ICU] monitoring and treatment). Asymptomatic patients with no clinical symptoms but positive RT-qPCR results were also admitted to the hospital. At the time of writing, all of the patients were discharged.

2.3 | Data collection

The data of the 129 COVID-19 cases from the two groups were extracted from the cloud database. Medical record reviews of the patients were performed to collect the patients’ underlying medical conditions, laboratory test results, and hospital course. In addition, epidemiological data of the patients were collected. The antibody levels of all patients were followed up to the 4th week after diagnosis. A total of 20 patients, 10 in each group were followed up to 8 weeks after diagnosis because of longer viral shedding time and hospital stays.

2.4 | Laboratory testing

Oropharyngeal swabs, nasopharyngeal swabs, or sputum specimens obtained from the patients during their hospital stay were collected for RT-qPCR testing. RT-qPCR was conducted using a commercial SARS-CoV-2 nucleic acid test kit (BioGerm) with fluorescence PCR detection equipment following the manufacturers’ instructions. The results are shown as the cycle threshold (Ct) for the ORF1ab and N genes of SARS-CoV-2. Corresponding serum samples were tested for anti-SARS-CoV-2 antibodies using a chemiluminescence immunoassay (CLIA; Bioscience).

2.5 | Whole-genome sequencing and analysis

Selected swab samples of the patients were then sent to the Beijing CDC for further whole-genome sequencing. Viral RNA was extracted using the Kingfisher Flex Purification System (Thermo Fisher), and libraries were
prepared using the Nextera XT Library Prep Kit (Illumina). The resulting DNA libraries were sequenced on a MiniSeq platform (Illumina) using a 300-cycle reagent kit. Mapped assemblies were generated using the SARS-CoV-2 genome (accession number NC_045512) as a reference. Variant calling, genome alignment, and sequence illustrations were generated with CLCBio software. Whole-genome sequence alignment was conducted using the Muscle tool in MEGA (v7.0). A neighbor-joining phylogenetic tree was constructed using MEGA (v7.0), and the Kimura 2-parameter model with 1000 bootstrap replicates was used. Genomic lineage designation was performed using the "PANGO lineage" typing method (https://cov-lineages.org/).

2.6 Statistical analysis

The statistical analyses were performed using SPSS version 25.0 (SPSS IBM). The demographic and clinical variables of each patient were included in the analysis. Normal continuous variables are represented by the mean and standard deviation. Student’s t-test was used to test for significant differences. Nonnormally distributed continuous variables are expressed as medians and interquartile ranges, and the Mann-Whitney U test was used for comparisons. Categorical variables are expressed as numbers and percentages, and the χ² test and Fisher’s exact test were used for comparisons. All tests were two-tailed, and statistical significance was defined as a p value lower than 0.05.

3 RESULTS

3.1 Basic information of the COVID-19 cases

Of the 129 cases, 8 (6%) were indigenous cases with one chain of transmission from China, and the remaining 121 (94%) were imported cases from outside China (Table 1). There were 88 (68%) cases of breakthrough infections and 41 (32%) cases of infections in unvaccinated individuals. There were 61 (69%) males and 27 (31%) females in the breakthrough infections group and 28 (68%) males and 13 (32%) females in the unvaccinated group (Table 2).

3.2 Whole-genome sequencing and analysis

Clinical samples from all 129 COVID-19 cases were acquired for further sequencing. Since the viral loads were relatively low in the tested samples, a total of 33 whole-genome sequences had genome coverage of over 98%, comprising 16 (18%) samples from the breakthrough infections group and 17 (41%) samples from the unvaccinated group. After confirming the sequences of the samples by the Pangolin COVID-19 Lineage Assigner Web application (https://pangolin.cog-uk.io/), the 33 strains contained four kinds of variants, including three kinds of VOCs (alpha, beta, and Delta variants) and lineage AZ.2 (sub-lineage of lineage B.1.1.318, which is currently designated "variants under monitoring (VUM)" by the WHO). Among the 16 SARS-CoV-2 strains from the breakthrough infections group, all strains except one were Delta variants, and one sample contained the alpha variant. There were two alpha, two beta, and eight Delta variants in the unvaccinated group and five strains from lineage AZ.2 (Table 3). The phylogenetic tree showed that most of the strains did not cluster together within the same lineage, which shows that the strains were from different countries of origin (Figure 1). The indigenous cases (indicated by a yellow arrow) clustered together because they were related cases. Furthermore, the AZ.2 strains were all imported from Greece, and they formed a clade with a high bootstrap value.

The numbers of nucleotide mutations (including substitutions, insertions, and deletions) of the Alpha, Beta, Delta, and AY.2 variants ranged from 53 to 66, 50 to 53, 42 to 63, and 67 to 73, respectively. The numbers of amino acid mutations within the spike protein ranged from 11 to 12, 12 to 13, 8 to 15, and 7 to 8, which is suggestive of a high rate of mutation.

3.3 Comparison of the general information and basic laboratory test results of the two groups

The median age of the breakthrough infections group was 33 (26, 38) years, and the median age of the unvaccinated group was 30 (23, 43) years, with no significant difference observed between the two

| Country of origin | Breakthrough infections (n = 88) | Unvaccinated group (n = 41) |
|-------------------|---------------------------------|-----------------------------|
| China             | 6 (7%)                          | 2 (5%)                      |
| Russia            | 1 (1%)                          | 3 (7%)                      |
| United States of America | 4 (6%) | 0                  |
| United Kingdom    | 6 (7%)                          | 5 (12%)                     |
| Sweden            | 2 (2%)                          | 2 (5%)                      |
| Denmark           | 2 (2%)                          | 1 (2%)                      |
| Italy             | 0                               | 1 (2%)                      |
| Greece            | 0                               | 6 (15%)                     |
| Hungary           | 1 (1%)                          | 0                           |
| Serbia            | 4 (6%)                          | 0                           |
| United Arab Emirates | 23 (26%) | 12 (29%)                  |
| Philippines       | 28 (32%)                        | 9 (22%)                     |
| Lebanon           | 1 (1%)                          | 0                           |
| Turkmenistan      | 3 (3%)                          | 0                           |
| Mongolia          | 2 (2%)                          | 0                           |
| Sudan             | 1 (1%)                          | 0                           |
| Senegal           | 1 (1%)                          | 0                           |
| Zimbabwe          | 2 (2%)                          | 0                           |
| Papa New Guinea   | 1 (1%)                          | 0                           |
Two patients from each group had underlying diseases. The average body mass index (BMI) of the breakthrough infections group was 23.59 ± 3.75 kg/m², and that of the unvaccinated group was 23.46 ± 4.57 kg/m², also with no significant difference between the two groups. There were also no differences in terms of sex, age, underlying diseases, or BMI between the two groups (Table 2).

Moreover, there were no significant differences in the laboratory tests between the two groups. The laboratory values analyzed included the leukocyte count, lymphocyte count, C-reactive protein (CRP) level, serum amyloid A (SAA) level, alanine aminotransferase (ALT) level, aspartate aminotransferase (AST) level, creatine kinase (Cr) level, prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), and fibrinogen level (Table 2). However, the average neutrophil count and D-dimer level in the unvaccinated group were higher than those in the breakthrough infections group, but they were all within the normal range.

The CD4 + T lymphocyte count, CD8 + T lymphocyte count, B lymphocyte count, and NK cell count were all lower in the unvaccinated group. The CD4 + T lymphocyte count was 580 (378.25, 866.75) cells/µl, which was much lower than that of the breakthrough infection group (821.84 ± 364.98 cells/µl), with a significant difference observed between the two groups (p = 0.018) (Table 2).

### 3.4 Comparison of the clinical severity level between the two groups

The two groups of patients mainly had either asymptomatic or mild cases; there were 64 (73%) asymptomatic patients and 7 (8%) mild patients in the breakthrough infections group and 25 (61%) asymptomatic patients and 5 (12%) mild patients in the unvaccinated group, with no significant differences observed between the two groups (p = 0.179 and p = 0.518). There were 17 and 9 patients with
moderate cases in the two groups, also with no significant differences observed \((p = 0.729)\). Two patients in the unvaccinated group developed the severe disease (severe or critical), whereas no patients in the breakthrough infections group had severe disease (Table 4).

### Table 3 Information on 33 COVID-19 patients whose sample was successfully sequenced

| Group                  | Countries of origin | Date of admission | Sequence ID             | Pango lineage/variant | Variant type |
|------------------------|---------------------|-------------------|-------------------------|-----------------------|--------------|
| Breakthrough infections| Serbia              | 2021/6/10         | SARS-CoV-2/Beijing/074/2021 | B.1.1.7/Alpha       | VOC          |
|                        | UK                  | 2021/6/16         | SARS-CoV-2/Beijing/077/2021 | B.1.617.2/Delta     | VOC          |
|                        | United Arab Emirates| 2021/7/16         | SARS-CoV-2/Beijing/083/2021 | AY.12/Delta        | VOC          |
|                        | United Arab Emirates| 2021/7/18         | SARS-CoV-2/Beijing/085/2021 | AY.12/Delta        | VOC          |
|                        | China               | 2021/7/29         | SARS-CoV-2/Beijing/089/2021 | B.1.617.2/Delta    | VOC          |
|                        | United States of America | 2021/7/27     | SARS-CoV-2/Beijing/092/2021 | B.1.617.2/Delta    | VOC          |
|                        | China               | 2021/8/2          | SARS-CoV-2/Beijing/096/2021 | AY.6/Delta         | VOC          |
|                        | China               | 2021/8/4          | SARS-CoV-2/Beijing/101/2021 | AY.12/Delta        | VOC          |
|                        | China               | 2021/8/4          | SARS-CoV-2/Beijing/102/2021 | B.1.617.2/Delta    | VOC          |
|                        | United Arab Emirates| 2021/8/7          | SARS-CoV-2/Beijing/105/2021 | B.1.617.2/Delta    | VOC          |
|                        | China               | 2021/8/4          | SARS-CoV-2/Beijing/107/2021 | B.1.617.2/Delta    | VOC          |
|                        | United Arab Emirates| 2021/8/4          | SARS-CoV-2/Beijing/108/2021 | B.1.617.2/Delta    | VOC          |
|                        | United States of America | 2021/8/14        | SARS-CoV-2/Beijing/111/2021 | B.1.617.2/Delta    | VOC          |
|                        | Turkmenistan        | 2021/8/19         | SARS-CoV-2/Beijing/113/2021 | B.1.617.2/Delta    | VOC          |
|                        | Sweden              | 2021/8/21         | SARS-CoV-2/Beijing/122/2021 | AY.4/Delta        | VOC          |
|                        | Turkmenistan        | 2021/8/22         | SARS-CoV-2/Beijing/124/2021 | B.1.617.2/Delta    | VOC          |
| Unvaccinated           | Greece              | 2021/6/4          | SARS-CoV-2/Beijing/066/2021 | AZ.2               | VUM          |
|                        | Greece              | 2021/6/4          | SARS-CoV-2/Beijing/067/2021 | AZ.2               | VUM          |
|                        | Italy               | 2021/6/1          | SARS-CoV-2/Beijing/068/2021 | B.1.1.7/Alpha      | VOC          |
|                        | Greece              | 2021/6/8          | SARS-CoV-2/Beijing/069/2021 | AZ.2               | VUM          |
|                        | Greece              | 2021/6/8          | SARS-CoV-2/Beijing/070/2021 | AZ.2               | VUM          |
|                        | UK                  | 2021/6/10         | SARS-CoV-2/Beijing/073/2021 | B.1.1.7/Alpha      | VOC          |
|                        | Greece              | 2021/6/11         | SARS-CoV-2/Beijing/076/2021 | AZ.2               | VUM          |
|                        | Philippines         | 2021/7/7          | SARS-CoV-2/Beijing/078/2021 | B.1.351/Beta       | VUM          |
|                        | Greece              | 2021/7/12         | SARS-CoV-2/Beijing/080/2021 | B.1.351/Beta       | VUM          |
|                        | UK                  | 2021/7/16         | SARS-CoV-2/Beijing/082/2021 | AY.4/Delta        | VOC          |
|                        | United Arab Emirates| 2021/7/16         | SARS-CoV-2/Beijing/084/2021 | B.1.617.2/Delta    | VOC          |
|                        | United Arab Emirates| 2021/7/16         | SARS-CoV-2/Beijing/084/2021 | B.1.617.2/Delta    | VOC          |
|                        | Philippines         | 2021/8/1          | SARS-CoV-2/Beijing/090/2021 | B.1.617.2/Delta    | VOC          |
|                        | China               | 2021/8/1          | SARS-CoV-2/Beijing/099/2021 | B.1.617.2/Delta    | VOC          |
|                        | Sweden              | 2021/8/8          | SARS-CoV-2/Beijing/104/2021 | B.1.617.2/Delta    | VOC          |
|                        | Philippines         | 2021/8/10         | SARS-CoV-2/Beijing/106/2021 | B.1.617.2/Delta    | VOC          |
|                        | UK                  | 2021/8/20         | SARS-CoV-2/Beijing/112/2021 | AY.4/Delta        | VOC          |

Abbreviations: COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; VOC, variants of concern; VUM, variants under monitoring.

#### 3.5 Comparison of the viral shedding time, Ct value, and IgM and IgG levels between the two groups

The median time from complete vaccination to the first positive nucleic acid test was 100.50 (24.00, 171.50) days. The median
duration of viral shedding was 3.00 (1.00, 11.75) days in the breakthrough infections group and 11.00 (2.00, 23.50) days in the unvaccinated group, showing a significant difference between the two groups ($p = 0.003$). The viral shedding time in the breakthrough infections group was significantly shorter than that in the unvaccinated group. At admission, there were no significant differences between the two groups regarding the median Ct values of the ORF1ab gene and N gene ($p = 0.267$ and $p = 0.148$) (Table 5). The median titer of IgM in the breakthrough infections group was 0.52 (0.14, 1.12), higher than the unvaccinated group, 0.25 (0.05, 0.86). The IgG titer ranged from 0.45 to 393.24 in the breakthrough infections group, with a median of 21.85 (9.56, 65.35), 1.1.72

FIGURE 1 Neighbor-joining phylogenetic tree based on the whole genome sequences of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The strains from the vaccine breakthrough infections are indicated with red font, while the strains from unvaccinated infections are indicated with blue font. The PANGO lineages are marked and colored on the right. The tree was rooted using strain WH04 (EPI_ISL_406801) in accordance with the root of the PANGO tree.
which was significantly higher than that in the unvaccinated group ($p = 0.000$) (Table 5). The IgG titers of the two patients in the unvaccinated group with severe disease were negative at admission.

3.6 Dynamic comparison of IgM and IgG levels of COVID-19 patients in the two groups

IgM and IgG levels of COVID-19 patients in the two groups were tested at admission and follow-up 4 weeks after admission. The IgM titers of patients with breakthrough infections declined after peaking during the second week after admission, while in the unvaccinated group, the IgM titers reached a peak at the third week. The IgG titers in the breakthrough infections increased rapidly after admission and reached a stable high level 2 weeks after admission. In the contrast, The IgG titers in the unvaccinated infections had a small increase and keep a relatively low level 2 weeks after admission without a clear peak in the 4-week-data. Of all the patients at admission and follow-up 4 weeks after admission, the IgG titers in the breakthrough infections group were significantly higher than those in the unvaccinated group ($p = 0.007$) (Figure 2).

Furthermore, there were 20 patients who were followed up to 8 weeks after diagnosis because they had longer viral shedding time and hospital stays. The IgG titers of these 20 patients (10 from each group) were tested follow-up 8 weeks after admission. The IgG titers in the breakthrough infections group increased rapidly after admission and reached a peak two weeks after admission, while the IgG titers in the unvaccinated group gradually increased till the fourth week after admission. A significant difference in IgG titers was also observed between the two groups ($p = 0.001$) (Figure 2).

3.7 Comparison of the vaccines from different platforms

Among the 88 patients with breakthrough infections, 42 (48%) were vaccinated with the Sinopharm BBIBP vaccine, 32 (36%) were vaccinated with the Sinovac CoronaVac vaccine, 4 (5%) were vaccinated with the Pfizer vaccine (BNT162B2), 1 (1%) was vaccinated with the AstraZeneca vaccine, and 1 (1%) was vaccinated with the Sputnik V vaccine. For 8 (9%) patients, the type of vaccine was unknown.

We compared the two Chinese inactivated vaccines and found that there were fewer asymptomatic infections and more patients with moderate disease among those who had received the Sinopharm BBIBP vaccine than among those who had received the Sinovac CoronaVac vaccine, with a significant difference observed between the two groups ($p = 0.020$ and $p = 0.009$). However, the time from full vaccination to the first positive nucleic acid test (days) between the vaccinees of the two different vaccines in the breakthrough infections group was significantly different. Individuals who received Sinopharm BBIBP had a much longer time from full vaccination to first positive nucleic acid test (176.79 ± 95.53 days) than those who received Sinovac CoronaVac (23.50 (15.50, 75.25) days) ($p < 0.001$). The Ct value, serum antibody titers, and viral shedding time were similar between the groups (Table 6).

3.8 Characterization of Delta variant infections within the 33 patients

Among the 33 patients whose samples were successfully sequenced, 23 were infected with Delta variants, including 15 (94%) from the breakthrough infections group and 8 (47%) from unvaccinated group.
(p = 0.007), indicating a significant difference. The IgM and IgG titers in patients with breakthrough infections were higher than those in patients without breakthrough infections (p = 0.007 and p = 0.001) as expected (Table 7). However, among the 23 patients infected with Delta variant, no significant differences in the Ct values of the ORF1ab and N genes and viral shedding time between the two groups were observed (p = 0.857 and 0.794 and p = 0.352, respectively).

Of all the breakthrough infections with successfully sequenced whole-genomes (16 cases), only one case was infected with other variant (Alpha), thus statistical analysis could not be conducted. The related data was indicated in Table S1. There were no significant differences in clinical severity level, Ct values of the ORF1ab and N genes, and viral shedding time between eight patients infected with Delta variants and nine patients infected with the other variants in the unvaccinated group (Table S2).
DISCUSSION AND CONCLUSION

Many studies have indicated that SARS-CoV-2 variants, especially VOCs, have obtained increased transmissibility, higher infectivity, and virulence. In addition, some kinds of variants not only have decreased susceptibility to antivirals and monoclonal antibodies but also have reduced neutralizing capacity with sera from convalescent patients and vaccinated individuals. Many key amino acid mutations on the Spike protein, especially on the receptor-binding domain (RBD) and the furin cleavage site, may result in varying degrees of immune escape. Therefore, it is highly possible for variants to cause breakthrough infections. In January 2021, breakthrough infections were first reported in Pfizer-BioNTech vaccinees in Israel. Subsequently, with the pandemic of Alpha, Delta, Omicron and other variants, more and more countries have reported different types of vaccine breakthrough cases. In China, despite strict prevention and control measures and high vaccination coverage rates, occasional breakthrough infections were detected. Our study summarized the genomic, immunological and clinical features of COVID-19 vaccine breakthrough infections in Beijing, China from June 1 to August 22, 2021, and achieved some beneficial results.

In this study, we excluded Pediatric patients because they commonly experience milder illness and atypical clinical manifestations and rarely have lymphopenia. We characterized 88 fully vaccinated patients experiencing SARS-CoV-2 breakthrough infections, most of the patients were either asymptomatic or had a mild case of COVID-19; no patients progressed to severe disease. The Ct values of the ORF1ab gene and the N gene between the patients with breakthrough infections and the unvaccinated patients were similar, however, the average duration of viral shedding in patients with breakthrough infections was much lower than that in unvaccinated patients. These data indicate that once breakthrough infections emerged, although vaccination may not reduce the amount of virus replication at the upper respiratory tract (oropharyngeal and nasopharyngeal), it can shorten the duration of virus shedding, which is also important for recovering from COVID-19 disease and of reducing transmission to others.

Similar findings have been reported in other studies. During July 2021, 469 cases of COVID-19 were identified among Massachusetts residents; the vaccination coverage among eligible Massachusetts residents was 69%. Approximately three-quarters (346; 74%) of

| TABLE 6 | Comparison of the Sinopharm BBIBP vaccine and the Sinovac CoronaVac vaccine |
|-----------------------------------------------|-------------------------------|-----------------|-----------------|
| | Sinopharm BBIBP (n = 42) | Sinovac CoronaVac (n = 32) | p value |
| Asymptomatic disease | 25 (60%) | 27 (84%) | 0.020 |
| Mild disease | 4 (10%) | 3 (9%) | 1.000 |
| Moderate disease | 13 (31%) | 2 (6%) | 0.009 |
| Ct value of the ORF1ab gene | 35.80 (32, 37.22) | 36.02 (27.89, 38.86) | 0.495 |
| Ct value of the N gene | 34.70 (31.99, 37.3) | 36.33 (28.1, 37.43) | 0.543 |
| IgM titer | 0.67 (0.13, 1.65) | 0.45 (0.16, 1.34) | 0.513 |
| IgG titer | 32.04 (5.73, 108.28) | 16.19 (9.14, 22.92) | 0.111 |
| Viral shedding time (days) | 3.00 (1.00, 11.50) | 3.00 (1.00, 12.00) | 0.699 |
| Time from full vaccination to first positive nucleic acid test (days) | 176.79 ± 95.53 | 23.50 (15.50, 75.25) | <0.001 |

| TABLE 7 | Comparison of patients with breakthrough infections and unvaccinated patients with the Delta variant |
|-----------------------------------------------|-------------------------------|-----------------|-----------------|
| | Breakthrough infections with the Delta variant (n = 15) | Unvaccinated patients with the Delta variant (n = 8) | p value |
| Asymptomatic disease | 3 (20%) | 2 (25%) | 1.000 |
| Mild disease | 4 (27%) | 2 (25%) | 1.000 |
| Moderate disease | 8 (53%) | 4 (50%) | 1.000 |
| Ct value of the ORF1ab gene | 26.52 ± 6.52 | 26.05 ± 4.13 | 0.857 |
| Ct value of the N gene | 25.18 ± 6.41 | 24.44 ± 6.20 | 0.794 |
| IgM titer | 0.22 (0.08, 0.65) | 0.05 (0.03, 0.10) | 0.007 |
| IgG titer | 4.87 (0.93, 38.53) | 0.02 (0.02, 0.05) | 0.001 |
| Viral shedding time (days) | 22.11 ± 5.73 | 25.5 (25, 26) | 0.352 |
cases occurred in fully vaccinated persons (those patients who had completed a two-dose course of an mRNA vaccine). The Ct values were similar among the samples from fully vaccinated patients and those from patients who were not fully vaccinated. According to Bergwerk et al., 39 breakthrough cases were identified among fully vaccinated health care workers. They concluded that the occurrence of breakthrough infections of SARS-CoV-2 correlated with neutralizing antibody titers during the peri-infection period and that most breakthrough infections were mild or asymptomatic cases. In Guangzhou, China, 38 cases of imported COVID-19 strains were reported in patients who had received inactivated vaccines (Vero cells). Patients infected with SARS-CoV-2 after vaccination can produce IgG antibodies rapidly during the early stage of disease compared to those who did not receive an inactivated vaccine. A large amount of similar research works have indicated that COVID-19 vaccines still show an obvious advantage in averting severe symptoms, hospitalization, and deaths.

For patients in the breakthrough infections group, the median time from being fully vaccinated to having a positive RT-qPCR result was 100.5 days. The median IgG titer of patients with breakthrough infections was 21.85S/CO at admission, significantly higher than that in the unvaccinated group. This finding indicated that the antibodies might still be detected approximately 3 months after vaccination, or a quick immune response was generated by IgG+ memory B cell because of the vaccination. Unfortunately, we do not know the dynamics of IgG titers of these patients before their admissions, so whether the level of IgG titer at admission was due to the long-lasting specific IgG generated by the vaccine or the immune memory caused by the infection was not clear. However, it could be speculated that the existing antibodies of patients in the breakthrough infections group before admissions are not enough to protect against viral infection. Studies on the level of neutralizing antibodies (NAbs) produced by inactivated COVID-19 vaccines in the real world have shown that the positive rate of NAbs was the highest from 10 to 70 days after the second dose of vaccine, and the positive rate gradually decreased as time went by. In addition, Sinovac Biotech revealed that Nab titers generated by CoronaVac decreased to near or below the lower limit of seropositivity 6 months after the second dose; As to neutralizing antibody results in this study, unfortunately, due to the hospital’s strict rules on the handling and transfer of COVID-19-related samples, and lacking BSL-3 lab, the serum of patient after IgG/IgM test was disposed of immediately as infectious waste. Therefore, neutralization tests were not performed in this study. Nevertheless, many studies have indicated that there was a high linear correlation between COVID-19 NAbs and IgM/IgG antibodies in vaccinees and a positive correlation between neutralizing antibody titers and the level of IgG antibodies. Ren et al found a strong positive correlation between S/RBD-IgG levels and neutralizing antibodies, and N-IgG antibody levels showed a positive correlation with neutralizing antibody levels. Livia et al. revealed a notable statistical correlation between neutralization titers and IgG, IgM, and IgA responses against the receptor-binding domain of the spike protein. The above findings suggested that in cases where NAbs cannot be detected, IgG antibodies can be detected instead. Therefore it could be speculated that the neutralizing antibody titers have declined to below protective levels in the vaccinees with breakthrough infections. In addition, we also compared the two Chinese inactivated vaccines within the breakthrough infections group and found that patients who received Sinovac CoronaVac vaccines presented milder symptoms than patients who received Sinopharm BBIBP vaccines. However, it could not be ignored that those who received Sinopharm BBIBP had a much longer time from full vaccination to first positive nucleic acid test (176.79 ± 95.53 days) than those who received Sinovac CoronaVac (23.50 (15.50, 75.25) days). The protection ability of the two vaccines cannot be compared in this study because of the different lengths of time postvaccination. NAbs levels continue to vary over time after vaccination, near or below the lower limit of seropositivity 6 months after the second dose. We can speculate that the NAbs among Sinopharm BBIBP vaccines went through a decease because of much longer time after full vaccination.

Moreover, the IgG levels in the breakthrough infections group rapidly increased after admission and were significantly higher than those in the unvaccinated group, which could be predicted. Many studies have shown that B cells have been found to mediate immunological memory (memory B cells and plasma cells) in response to vaccination. Yuxin Chen et al. reported that CoronaVac induced robust circulating and memory B cell and T cell responses, and they observed a notable expansion of long-lasting, isotype-switched IgG memory B cells among virus-specific memory B cells following vaccination, which lasted for at least 6–8 weeks. The majority of the antibodies produced for a secondary response are IgG, not IgM, which dominates the early primary response; IgG antibodies also have a higher affinity for pathogens due to the process of somatic hypermutation. In addition, a recent study from JAMA indicated that total receptor-binding domain-specific immunoglobulin with breakthrough infections was significantly higher than participants without breakthrough infections but fully vaccinated, with a 322% high increase.

Besides, our study revealed that compared to the unvaccinated group, the breakthrough infections group had higher counts of CD4+ T lymphocytes, CD8+ T lymphocytes, B lymphocytes, and NK cells. T cell-mediated adaptive immune responses are essential for viral clearance and long-term antiviral immunity. Successful vaccines should generate SARS-CoV-2-reactive T cells with high specificity to elicit potent immune responses devoid of the undesired effects of inflammation or inception of disease. More and more studies have shown that cellular immunity plays a very critical role in preventing severe COVID-19 and deaths. Variants such as Delta, with many key mutations on the spike protein, may evade humoral immunity to cause breakthrough infections. However, most of the functional T cell epitopes have not been influenced by the viral mutation which immune system still remained comparable with T cell immunity to prevent the progression of the disease. Vaccines mainly target cellular immunity might be a new thought for COVID-19 vaccine design and development.
Delta variant is the fourth VOC designated by WHO, was first detected in India in December 2020, and became the most commonly reported variant starting in mid-April 2021.35 Mutations in the Delta variant may lead to higher replication rates, thereby increasing the viral load and transmission rate.41 Studies showed that Delta variant has exhibited some ability to evade the immune system as neutralizing antibodies from prior infections or vaccines are less receptive to binding with the S protein, eventually leading to breakthrough infections.37–40 In this study, the COVID-19 patients were admitted during the period when Delta variants were becoming predominant and co-circulating with other variants worldwide. We found that among the 33 fully sequenced whole-genomes of the samples from COVID-19 patients, Delta variants accounted for 94% (15/16) in the breakthrough infections group whereas 47% (8/17) were detected in the unvaccinated group, which showed a significant statistical difference. However, it could not be neglected that among Delta variant breakthrough infections, five cases were indigenous associated cases with one chain of transmission. Furthermore, in the unvaccinated group, the phylogenetic tree displayed a cluster composed of five strains from lineage A2.2, these five strains were all imported from Greece. With such a small number of samples, the above factors would contribute to a statistical bias of the result. Among all the Delta variants, there was no difference in the Ct values between the vaccinated and unvaccinated groups as well as no significant difference in the viral shedding time. For Ct values, our study was in line with some other studies. In PoYing Chia et al.’s study, their initial viral load indicated by PCR Ct value was similar between vaccinated and unvaccinated patients with B.1.617.2.41 Another study demonstrated that fully vaccinated individuals with breakthrough infections have a similar viral load as unvaccinated patients.42 Koen B et al. reported that with B.1.617.2, infections occurring after two vaccinations had a similar peak viral burden as those in unvaccinated individuals.43 Anika et al. reported that vaccination accelerated viral clearance,44 whereas there was no significant difference with viral shedding time between the two groups in our study. Some studies also showed that vaccination is associated with a faster decline in viral load in Delta variant.41 However, the small number of Delta variant patients in our study might affect the results so further research will be needed.

This study has some limitations that should be mentioned. First, the sample size was relatively small. Second, of the patients in the breakthrough infections group, the initial vaccination to the admission times were different, which may lead to statistical bias. Third, full genome sequencing results were not available for most patients, which may be related to the low viral load (high CT value) in some patients who tested negative in the country of origin. Also, the lacking whole-genome sequences also led to a very small sample size of known genotypes (16) within the breakthrough infections group, which resulted in difficulty of analyzing the difference between Delta breakthrough infections and Non-Delta breakthrough infections. Fourth, neutralization tests were not performed in this study, which is the biggest limitation, providing lessons for our further study.

In conclusion, our study summarized the features of COVID-19 vaccine-breakthrough cases in Beijing, China, and indicated that existing vaccinations do not confer full protection against SARS-CoV-2 infection, therefore precaution is still needed among vaccinated people. However, the efficacy of vaccines displayed an obvious advantage in reducing severe symptoms, hospitalization, and deaths. To prevent vaccine breakthrough infections, fully vaccinated populations should still practice preventive measures. Furthermore, many recent studies have indicated that a vaccine booster dose could rapidly recall a SARS-CoV-2-specific immune response, leading to a significant rebound in antibody levels, which promotes high effectiveness against circulating variants such as Delta to prevent breakthrough infection.20,45–48 Therefore, universal booster vaccination could be a current strategy to prevent breakthrough infections from COVID-19.

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CONFLICT OF INTERESTS
The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS
Zhihai Chen and Wenbo Xu conceived the study. Wenbo Xu and Zhihai Chen designed the study. Zhihai Chen and Wenbo Xu, and Peng Yang maintained the database for data collection. Zhihai Chen and Wenbo Xu supervised the data collection. Di Tian, Yang Song, Man Zhang, Yang Pan, Ziruo Ge, Yao Zhang, Xingxiang Ren, Jing Wen, and Yanli Xu interpreted the data. Di Tian, Yang Song, and Man Zhang did the statistical analysis. Yang Song, Di Tian and Hong Guo prepared the manuscript. Di Tian, Yang Song, Man Zhang, and Ziruo Ge wrote the manuscript. Yang Song, Di Tian and Wenbo Xu revised the manuscript. Di Tian, Yang Song and Ziruo Ge prepared the figures. Man Zhang, Yang Pan, and Peng Yang performed the COVID-19 specimen processing and sequencing. Man Zhang, Yang Pan, Peng Yang and Yang Song analyzed the genome sequences, and all authors reviewed and approved the final version of the manuscript. Zhihai Chen, Wenbo Xu, and Peng Yang are the guarantors.

DATA AVAILABILITY STATEMENT
The sequence data generated in this study was available to researchers through GISAID database under the IDs of EPI_ISL_8582079, EPI_ISL_8582078, EPI_ISL_8582059, EPI_ISL_8582058, EPI_ISL_8582075, EPI_ISL_8582074, EPI_ISL_8582077, EPI_ISL_8582076, EPI_ISL_8582071, EPI_ISL_8582070, EPI_ISL_8582073, EPI_ISL_8582072, EPI_ISL_8582068, EPI_ISL_8582067, EPI_ISL_8582069, EPI_ISL_8582064, EPI_ISL_8582086, EPI_ISL_8582063, EPI_ISL_8582085, EPI_ISL_8582066, EPI_ISL_8582088, EPI_ISL_8582065, EPI_ISL_8582087, EPI_ISL_8582060, EPI_ISL_8582082, EPI_ISL_8582081, EPI_ISL_8582062, EPI_ISL_8582084, EPI_ISL_8582061, EPI_ISL_8582083, EPI_ISL_8582080, EPI_ISL_8607167 and EPI_ISL_8607166.
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SUPPORTING INFORMATION
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