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Short communication

Increased delta variant SARS-CoV-2 infections in a highly vaccinated medical center in Japan

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Abstract

The Delta variant has dominated SARS-CoV-2 infections in Tokyo, Japan from June 2021 to date. We conducted a retrospective cohort study to assess BNT162b2 vaccine effectiveness during the surge in Delta among 3,911 healthcare workers (HCWs) at a medical center of Tokyo with a high vaccination rate of 84.1%. With strict infection control protocols including universal masking, only a small number of cases among vaccinated and unvaccinated HCWs were identified before June. As Delta spread in Tokyo, 16 cases among 3,289 fully vaccinated HCWs and 11 cases among 574 unvaccinated HCWs were reported in July and August (case rate in August: 4.0 vs. 19.2 per 1,000). All breakthrough cases were confirmed as Delta. While our study confirms a robust vaccine effectiveness of BNT162b2 vaccine against Delta, rising breakthrough cases suggest that continued infection control measures are warranted in higher risk environments, even when high rates of vaccination coverage are achieved.

1. Introduction

Japan has experienced multiple waves of coronavirus disease 2019 (COVID-19) infections since the pandemic started and, as of mid-September 2021, is currently in its fifth wave. Compared to previous waves, record numbers of daily new cases have been confirmed, with a peak of 25,851 cases on August 20[1]. Vaccination rollout in Japan began with healthcare workers (HCWs) in mid-February 2021, starting with the BNT162b2 (Pfizer-BioNTech) mRNA vaccine, followed by the mRNA1273 (Moderna) vaccine in May 2021. Full vaccination (two doses) was achieved in 41.9% of the overall population by the end of August, with coverage reaching 88.3% of those over 65[2]. In contrast, vaccination for the younger and middle-aged individuals (aged 15–64 years old) has been slower with just 28.9% fully vaccinated by August 31[2].

Spread of the Delta variant has been observed across Japan, with a major outbreak first seen in Osaka in March, then reported in Tokyo by June 2021, causing increased number of daily confirmed cases. (Supplementary Materials) Since the first week of June, Delta gradually replaced other observed variants, accounting for over 90% of all PCR positive tests in the Tokyo metropolitan area by the end of August 2021[3]. Delta was the predominant variant in countries with high vaccination coverage, including the United Kingdom and Singapore[4,5]. This highly transmissible variant has also caused recent outbreaks in China, where vaccination coverage is high and infection control measures remain strict[6].

Previous studies have shown the Delta variant has increased transmissibility even in some fully vaccinated individuals[7,8]. Resurgence of SARS-CoV-2 infections has also been reported in medical centers with high rates of vaccination[9]. However, reports addressing Delta’s impacts on breakthrough infections among fully vaccinated individuals mainly come from North America and Europe, where the social dynamics of compliance with public health measures may differ from other parts of the world. Moreover, effectiveness of mRNA vaccines in ethnic groups of the Western Pacific region may also differ compared to populations in North America and Europe, as suggested by our recent report of increased reactogenicity among Japanese HCWs receiving BNT162b2 vaccines[10]. To explore these potential differences, we conducted a retrospective cohort study to assess BNT162b2 vaccine effectiveness during the Delta surge among HCWs at a tertiary level center with a high vaccination rate in Tokyo, Japan.

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2. Study methods

This retrospective cohort study assessed SARS-CoV-2 infections from March 1 to August 31, 2021 at Juntendo University Hospital (JUH), a multispecialty, 1051-bed tertiary level academic hospital in Tokyo, Japan that provides screening, diagnosis, and acute ward/ICU care for COVID-19 patients. A total of 3,911 registered JUH HCW employees who agreed to participate via web consent were included in the study. Relevant vaccination and infectious disease data were extracted from the electronic charts of each participant. On-site employee vaccinations with BNT162b2 began on March 17; the first batch from March 17 to April 23 for the first dose, and April 7 to May 19 for the second dose. mRNA-1273 vaccines were not available at JUH until September 1; employees who received mRNA-1273 during the study period were vaccinated in other facilities or mass vaccination centers managed by the central government of Japan.

Regarding infection control protocols, masks are mandated for employees at all times except while eating. Outside of work hours, dining with more than two non-family members is strongly discouraged. Temperature is checked and self-reported daily by all employees; those with temperature above 37.5°C are required to submit a PCR test for further examination. Additional PCR testing is conducted at the discretion of an employee health physician after clinical evaluation for classified close contacts, and/or those who have flu-like symptoms such as fatigue, cough, runny nose, etc. (Supplementary Materials) For further infection control, all patients visiting our hospital are strongly encouraged to wear face masks, with virtually universal compliance; free masks are provided to visitors without one. At the time of this study, all inpatients were required to take a COVID-19 PCR test prior to admission. Except in extenuating circumstances, visitors were not allowed onto wards.

For diagnosis of SARS-CoV-2 infection, nasopharyngeal and saliva tests, both showing high sensitivity and specificity in previous studies, were performed [11]. Nasopharyngeal swabs were performed following a standardized procedure (WHO 2006) [12]. For saliva sampling, the participants collected 1–2 mL of unstimulated saliva into a sterile 50-mL polyethylene tube. Nasopharyngeal swabs and saliva samples were submitted for RT-PCR testing within 3 h after collection [13]. RT-PCR was carried out using the 2019 Novel Coronavirus Detection Kit (nCoV-DK; Shimadzu Corporation, Kyoto, Japan). The nCoV-DK assay uses the “2019-nCoV_N1” primer and probe sequences as described by the U.S. CDC’s “2019-Novel Coronavirus Real-time rRT-PCR Panel Primers and Probes” [14]. This assay also includes internal control oligonucleotides. Real-time PCR analysis was run on a Light Cycler System (Roche, California, USA). Specific spike protein variations (L452R, N501Y, E484K, E484Q) were detected with the VirSNiP SARS-CoV-2 Mutation Assays (Roche Diagnostics, Rotkreuz, Switzerland) according to the manufacturer instructions. In addition, serological tests were conducted in June after two doses of vaccine. (Supplementary Materials)

The primary outcome of this study was case rate (attack rate) among fully vaccinated versus unvaccinated HCWs. In addition,

| Table 1 | Vaccination status, SARS-CoV-2 infections, and case rates among fully vaccinated and unvaccinated HCWs, March through August 2021. |
|---------|---------------------------------------------------------------|
|         | March | April | May | June | July | August |
| No. of health workers: 3,911* | | | | | | |
| Administered vaccines | | | | | | |
| BNT162b2 (Pfizer-BioNTech) | 2,804 | 390 | 33 | 53 | 20 | 14 |
| mRNA-1273 (Moderna) | 0 | 0 | 0 | 1 | 10 | 12 |
| Vaccination status (cumulative no. of staff) | | | | | | |
| Fully vaccinated | 47 | 2,866 | 3,172 | 3,221 | 3,261 | 3,289 |
| Partially vaccinated | 2,757 | 328 | 55 | 60 | 50 | 48 |
| Unvaccinated | 1,107 | 717 | 684 | 630 | 600 | 574 |
| Fully vaccinated workers (%) | 1.2 | 73.3 | 81.1 | 82.4 | 83.4 | 84.1 |
| Workers receiving at least 1 dose of vaccine (%) | 71.7 | 81.7 | 82.5 | 83.9 | 84.7 | 85.3 |
| SARS-CoV-2 infections | | | | | | |
| Fully vaccinated workers | 0 | 0 | 0 | 0 | 0 | 0 |
| Partially vaccinated workers | 0 | 1 | 0 | 0 | 0 | 0 |
| Unvaccinated workers | 0 | 2 | 0 | 0 | 0 | 0 |
| Case rate (attack rate) per 1000 | | | | | | |
| Fully vaccinated workers (95% CI: confidence interval) | – | – | – | – | (0.00 to 0.52) | (0.17 to 1.05) |
| Unvaccinated workers (95% CI) | 0.0 | 2.8 | 0.0 | 0.0 | 0.0 | 19.2 |

Notes:
*No. of health workers comprises staff registered as Juntendo University Hospital employees by August 31, 2021.
*Bootstrap analysis was performed to determine the CIs (shown above).
detailed data on variant type, along with duration between full vaccination to infection and vaccine-induced anti-S IgG levels, were analyzed to more thoroughly assess the impacts of the Delta variant and efficacy of vaccination. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 27 (IBM Japan). In addition, the bootstrap method (1000 replications) was used to produce the confidence interval (CI) for the case rate of infection. The CI is based on normal-theory, assuming that log(case rate) is normally distributed. This study was approved by Juntendo University Institutional Review Board (No. 2021055).

3. Results

Among 3,911 healthcare workers (mean age, SD; 36.6, [±11.8]) at JUH, 1,296 (33.1%) men and 2,615 (66.9%) women were enrolled in the study. Characteristics of the studied cohorts are shown in Supplementary Table 1. (Supplementary Materials)

By August 31, 2021, a cumulative number of 3,289 (84.1%) HCWs had received two doses of mRNA vaccine; 48 had received one dose and 574 remained unvaccinated. During the study period, 16 fully vaccinated HCWs were confirmed to have SARS-CoV-2 infection, 1 infection was identified among those partially vaccinated, and 13 infections were confirmed among unvaccinated HCWs. Monthly case rate among fully vaccinated and unvaccinated groups are presented in Table 1, with 95% CI of 0.17 to 1.05 and 1.05 to 2.97 for these two groups, respectively, in August 2021. Monthly case rates are also illustrated in Fig. 1-1. No hospitalization or deaths were reported.

L452R mutation, the most representative mutation of the Delta variant, was confirmed among all breakthrough cases occurring in July and August with available nasopharyngeal or saliva samples (13 out 16). (Table 2). Regarding infections in unvaccinated HCWs, except for one case with N501Y mutation, all cases with available nasopharyngeal or saliva samples were identified as having L452R mutation. (Figs. 1-2 and 1-3) The prevalence of Delta variant in JUH is shown in Fig. 2 and was consistent with that of the Tokyo metropolitan area. Among all reported positive tests, including PCR tests for non-employees such as inpatients before admission, the Delta variant comprised 88.9% of all cases, increasing to 98.0% after exclusion of cases in which nasopharyngeal or saliva samples were unavailable.

For the 16 breakthrough cases, none had known or confirmed infection prior to vaccine rollout in March 2021. A wide range of anti-S IgG levels, ranging from 417 to 3,793 U/ml (mean, SD; 1,405, [±1,122]), were reported for these cases. Ct (threshold cycle) values of RT-PCR positive cases with available nasopharyngeal or saliva samples ranged from 16.60 to 33.00 (mean, SD; 24.16, [±5.88]). (Table 2) For the 14 non-breakthrough cases, results of serological tests and Ct values are provided in Supplementary Materials.

4. Discussion

During the Delta spread, our study of HCWs working in a highly vaccinated medical environment with strict infection control protocols identified a number of SARS-CoV-2 infections in recent months regardless of vaccination status. Nonetheless, the case rate among those fully vaccinated was substantially lower compared to those unvaccinated at 4.0 vs. 19.2 per 1,000 persons, respectively, in August 2021. No hospitalizations or deaths were reported for either group. Our findings are consistent with previous studies that the BNT162b2 vaccine remains effective against Delta, protecting vaccinated individuals from severe infections and hospitalization [5].

With strict infection control protocols such as universal masking and actively encouraging employees to minimize social events, few infections among HCWs were reported before June when the wild-type, Alpha, and other variants dominated the Tokyo Metropolitan area. In contrast, with the rapid spread of the Delta variant beginning in mid-June, several infections occurred throughout July and August, even among fully vaccinated individuals. A previous retrospective cohort study in Singapore reported lower Ct values and longer viral shedding associated with the Delta variant, suggesting increased transmissibility [8]. Although the correlation between Ct values and the amount of virus per specimen is imperfect, our study showed relatively low Ct values associated with the Delta variant among the vaccinated HCWs, supporting the findings of the Singapore study [8,15].

The breakthrough cases found in our study received two doses of the BNT162b2 vaccine in March and April, with an average of less than four months between full vaccination and infection, shorter than the six month period currently being considered for...
booster vaccines [16]. Marginally diminished vaccine effectiveness against Delta has been reported in several previous studies, and is corroborated in our population [17,18]. The breakthrough cases found in our highly vaccinated medical center are likely to be the result of a combination of marginally lower vaccine effectiveness against Delta and increased transmissibility of the variant. However, even during Delta spread, our overall breakthrough case numbers remained low. Strict infection control protocols including universal masking were continued even after implementation of our vaccination program. Effectiveness of face masks in preventing airborne transmission and reducing SARS-CoV-2 cases has been shown in multiple previous studies, and many governmental and professional organizations continue to recommend indoor mask-wearing to prevent COVID-19 infections during Delta spread [19,20]. Strict universal masking has likely contributed to overall lower surge numbers in the Japanese setting.

### Table 2

Confirmed breakthrough SARS-CoV-2 infections from March through August 2021.

| Cases | Sex | Age | 1st dose | 2nd dose | Date of infection confirmed | PCR Testing methods | Days from the 2nd dose | Break-through cases | Ct value | Mutation | IgG level testing date | Anti-S (U/ml) |
|-------|-----|-----|----------|----------|-----------------------------|--------------------|----------------------|---------------------|----------|-----------|----------------------|--------------|
| Case 1 | F   | 43  | 2021/03/23 | 2021/04/13 | 2021/07/05 | Saliva | 83 | Yes | 22.40 | L452R | 2021/6/11 | 417 |
| Case 2 | M   | 45  | 2021/03/17 | 2021/04/07 | 2021/07/24 | Nasopharyngeal | 108 | Yes | 30.74 | L452R | 2021/6/9 | 477 |
| Case 3 | F   | 29  | 2021/03/19 | 2021/04/09 | 2021/07/24 | Nasopharyngeal | 106 | Yes | 20.08 | L452R | 2021/6/10 | 1,476 |
| Case 4 | F   | 43  | 2021/03/30 | 2021/04/20 | 2021/08/03 | – | 105 | Yes | – | – | 2021/6/18 | 976 |
| Case 5 | F   | 26  | 2021/03/23 | 2021/04/13 | 2021/08/05 | Saliva | 114 | Yes | 22.00 | L452R | 2021/6/11 | 3,713 |
| Case 6 | M   | 31  | 2021/04/03 | 2021/04/23 | 2021/08/05 | Saliva | 104 | Yes | 18.96 | L452R | 2021/6/16 | 518 |
| Case 7 | F   | 24  | 2021/03/24 | 2021/04/14 | 2021/08/07 | – | 115 | Yes | – | – | 2021/6/18 | 1,459 |
| Case 8 | F   | 28  | 2021/04/22 | 2021/05/13 | 2021/08/10 | Saliva | 89 | Yes | 29.65 | L452R | 2021/6/8 | – |
| Case 9 | M   | 46  | 2021/03/23 | 2021/04/13 | 2021/08/15 | – | 124 | Yes | – | – | 2021/6/17 | 1,113 |
| Case 10 | M  | 32  | 2021/03/22 | 2021/04/12 | 2021/08/16 | Nasopharyngeal | 126 | Yes | 20.66 | L452R | 2021/6/11 | 1,282 |
| Case 11 | F   | 23  | 2021/03/25 | 2021/04/15 | 2021/08/17 | Nasopharyngeal | 124 | Yes | 29.09 | L452R | 2021/6/8 | 3,793 |
| Case 12 | F   | 22  | 2021/04/22 | 2021/05/20 | 2021/08/18 | Saliva | 97 | Yes | 32.42 | L452R | 2021/6/16 | – |
| Case 13 | F   | 25  | 2021/03/23 | 2021/04/13 | 2021/08/19 | Nasopharyngeal | 128 | Yes | 18.30 | L452R | 2021/6/9 | 761 |
| Case 14 | F   | 24  | 2021/03/25 | 2021/04/15 | 2021/08/21 | Nasopharyngeal | 128 | Yes | 20.20 | L452R | 2021/6/14 | 1,683 |
| Case 15 | F   | 49  | 2021/03/24 | 2021/04/14 | 2021/08/21 | Nasopharyngeal | 129 | Yes | 16.60 | L452R | 2021/6/16 | 594 |
| Case 16 | F   | 42  | 2021/03/24 | 2021/04/14 | 2021/08/25 | Saliva | 133 | Yes | 33.00 | L452R | 2021/6/9 | – |

Notes:

*All received BNT162b2 mRNA COVID-19 vaccine.

PCR testing method and variant details are not available for cases that were tested at facilities outside of JUH, but reported via JUN's monitoring system.

Breakthrough cases are defined as infections at least 14 days after receiving second vaccination.

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**Fig. 2.** PCR positive cases with L452R mutation (Delta variant) as % of total positive cases in JUH, March through August 2021.
Limitations

There are several limitations to our study worth addressing. First, although PCR testing is performed for those reporting temperature above 37.5 °C during daily checks, close contacts of confirmed cases, and/or those having flu-like symptoms, asymptomatic cases may be missed; therefore, actual case rate are likely underestimated in our results. Second, due to overall low case rates in this hospital, prior infections among all healthcare workers not infected during the studied period were not analyzed in this study. However, all studied breakthrough cases were checked and found not to have prior infections. Lack of analysis on acquired immunity via prior infections among all healthcare workers might have underestimated the vaccine effectiveness. Third, although the strict infection control measures implemented in this tertiary level hospital may represent the general compliance of Japanese citizens at large, the level of control in the healthcare workplace setting is likely higher than average; our findings are particularly applicable to high-risk healthcare environments and extrapolation to the general population should be interpreted with caution.

5. Conclusion

Our retrospective cohort study provides real-world evidence of maintained robust BNT162b2 vaccine effectiveness against Delta in an Asian population, yet also revealed increased breakthrough cases in this highly vaccinated medical center. With demand for vaccinations in Japan continuing at a strong pace, all individuals willing to receive COVID-19 vaccines are expected to be fully vaccinated by the end of November 2021; rapid vaccination programs are expected in other countries of the Western Pacific region in the coming months as well. Nonetheless, our findings emphasize the need for ongoing vigilance toward breakthrough infections despite an environment with high vaccination coverage and strict public health protocols. From a public health policy perspective, given the current prevalence of the Delta variant and the possible future emergence of highly transmissible variants, our data suggest that infection control measures such as masking, personal hygiene, and social distancing will continue to be required in high-risk settings.

Authorship statement

Prof Naito had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of data analysis.

Concept and design: All authors.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Yan, Deshpande, Naito.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Ito, Tabe, Nojiri, Seyama.

Administrative, technical, or material support: Tabe, Seyama, Takahashi.

Supervision: Naito, Takahashi.

All authors meet the ICMJE authorship criteria.

Conflict of interest statement

The authors declare no conflict of interest.

Ethical statement

Study protocol was approved by the Institutional Review Board (IRB) of Juntendo University Faculty of Medicine, Juntendo University. (No. 2021055) All participants agreed to participate in this study.

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CRediT authorship contribution statement

Toshio Naito: Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2022.04.029.

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