Effectiveness of mRNA COVID-19 Vaccines in Japan During the Nationwide Pandemic of the Delta Variant

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**Running title:** Effectiveness of COVID-19 vaccines in Japan

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ABSTRACT

The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), remained a major global health concern in 2021. To suppress the spread of infection, mass vaccinations have been performed in countries worldwide. In Japan, vaccinations of the first and second doses for most of the nation were performed during the nationwide outbreak of the B.1.617.2 (Delta) variant with the L452R spike protein mutation, and the effectiveness of the vaccinations to suppress the spread of COVID-19 among the people in Japan remains uncertain. In this study, adults aged ≥18 years, who were in contact with patients with COVID-19 and underwent nasopharyngeal swab reverse transcription-polymerase chain reaction (RT-PCR) test in August and September 2021 at a mass screening test center in Japan, were enrolled. In this period, more than 95% of the COVID-19 infection was reported to be caused by the Delta variant. As a result, a total of 784 adults with recent contact history, including 231 (29.5%) RT-PCR test-positive cases, were enrolled. The test positive rate was lower in individuals who had been vaccinated twice than in those who had not been vaccinated (12.5% vs. 39.0%, p<0.0001), with the risk ratio of 0.32 (95% confidence interval: 0.23–0.46). The effectiveness of vaccines was highest after 7 to 90 days from the second vaccine dose. In conclusion, two doses of mRNA COVID-19 vaccines were effective for suppressing the transmission in Japan during the nationwide pandemic of the Delta variant, estimated to have prevented 50%-80% of the infection.
Keywords: coronavirus disease 2019 (COVID-19), Delta variant, L452R spike protein mutation, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), mRNA vaccines
1. Introduction

The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), still remained a major global health concern in 2021 (Fontanet et al. 2021; Skegg et al. 2021). As of August 2021, more than 200 million individuals worldwide have been infected by the virus, and more than four million have died because of the infection. Recently, the world has struggled with the spread of the B.1.617.2 (Delta) and B.1.1.529 (Omicron) variants, both of which have been classified as variants of concern by the Centers for Disease Control and Prevention (Del Rio et al. 2021; Planas et al. 2021).

Since July 2021, Japan has faced the fifth wave of the pandemic, the largest to date. The major prevailing viral strain has been the Delta variant with L452R spike protein mutation. In parallel to the Delta variant pandemic, the central and local governments in Japan have collaboratively promoted mass vaccination for the nation with messenger RNA (mRNA) COVID-19 vaccines. Nearly half of the people in Japan completed two doses of vaccines by the end of August 2021. During the mass vaccination campaign, the vaccines have been known to effective for the original strain (Bian et al. 2021; Sheikh et al. 2021), but the effectiveness against the Delta variant remained uncertain (Lopez Bernal et al. 2021). The transmissibility of the Delta variant is known to be higher than that of the original strain, with increased potential to escape from neutralizing antibodies targeting the receptor-binding domain of the viral spike protein (Mleochova et al. 2021; Planas et al. 2021). Thus, the
effectiveness of mRNA vaccines against COVID-19 during the pandemic with the Delta variant is
with particular clinical and epidemiologic interests. This study aimed to determine the suppression
rate of COVID-19 transmission by the mRNA vaccines during the nationwide pandemic of the Delta
variant in Japan, by comparing the RT-PCR test positivity rate between those completed two doses of
vaccines and others.

2. Materials and methods

2.1. Participants

Adults aged ≥18 years who were in contact with patients with COVID-19 and underwent
nasopharyngeal swab reverse transcription-polymerase chain reaction (RT-PCR) test at a single
screening test center in Sendai city, Japan from August to September 2021 were enrolled. During the
study period, more than 95% of the COVID-19 patients in the locality were suggested to be infected
by the B.1.617.2 (Delta) variant, according to the sequencing results released from the Miyagi
Prefectural Government (https://www.pref.miyagi.jp/site/covid-19/02-02.html). For the enrolled
individuals, data on age, sex, completion status of COVID-19 vaccination, vaccine manufacturers,
closeness of contact, and RT-PCR test results were collected. The RT-PCR test positive rate was then
compared by closeness of contact and vaccine completion status.
2.2. Closeness of Contact

A history of close contact with COVID-19 patients is judged by the local government staff in public health centers. The close contact is currently judged by the fulfillment of all of the following four criteria in Japan: 1) contact with a COVID-19 patient from 2 days before to 14 days after the onset of symptoms or the positive RT-PCR test results; 2) not wearing masks; 3) contact involving < 1 m distance; and 4) ≥ 15 minutes of contact. If an individual is with the absence of one or more of these four criteria, the individual was judged to be with a low-risk contact.

2.3. RT-PCR Screening Test Methods

RT-PCR was performed by detecting the nucleocapsid protein set no. 2 (N2) gene, using the primer/probe set designed by the National Institute of Infectious Diseases in Japan (NIID_2019-nCoV_N_F2, R2, and P2) (Shirato et al. 2020). The reaction mixture comprised the primer/probe set for N2 detection, 4× TaqMan Fast Virus 1-Step Master Mix (Thermo Fisher Scientific, Waltham, MA, USA), and nuclease-free water. Details for the thermal cycling conditions were previously reported (Ishii et al. 2021).

2.4. Types of vaccines against COVID-19
Almost all the participants were vaccinated against COVID-19 by either of the following two types of vaccines manufactured by different pharmaceutical companies: BNT162b2 mRNA vaccine (Pfizer/BioNTech) or mRNA-1273 vaccine (Moderna). During the study period, people basically received two doses of the same type of vaccine. At the enrollment, the majority of the younger participants aged < 65 years did not complete two doses of vaccines, whereas most of the older participants aged ≥ 65 years completed two doses of vaccines. This was because the government gave vaccine priority to older people, and the vaccine rollout was started earlier for the older people.

2.5. Statistical Analysis

In each subgroup, the RT-PCR test positive rate was compared using the chi-square test and Fisher’s exact test, according to the size of each cell. The effectiveness of vaccination was further evaluated by calculating the risk ratios (RR) and their 95% confidence interval (CI) for RT-PCR test positivity in individuals who had been vaccinated twice compared to those who had not been vaccinated. Statistical significance was set at $P<0.05$.

2.6. Ethics approval

The Institutional Review Board of Tohoku University Graduate School of Medicine approved the present study (approval number: 2020-1-535). Written informed consent was waived to prevent the
risk of unnecessary transmission at the testing center, and informed consent was secured in an opt-out manner.

3. Results

3.1. Overall effectiveness

A flow diagram of the study design is shown in Fig. 1. Non-adults aged <18 years were not recruited in this study, as only 17 (1.5%) of the 1123 non-adults with contact history had completed two doses of vaccinations. A total of 784 consecutive adults (337 males and 447 females) with recent contact history with COVID-19 patients from August to September 2021, among whom 231 (29.5%) were RT-PCR test-positive, were enrolled. The distributions of age in the total participants and in the RT-PCR test positive cases are shown in Fig. 2A, 2B. Among the 784 participants, 240 (30.6%) were after the second vaccine dose, 72 (9.2%) were after the first dose and before the second dose, and 472 (60.2%) were not vaccinated at the timing of the RT-PCR test. Most of the older adults aged ≥65 years had already completed vaccination as the priority group during the study period, whereas most of the other younger adults had not (Fig. 2C, 2D). The RT-PCR test positive rate according to the completion status of COVID-19 vaccination in each population subgroup is summarized in Table 1. The test positive rate of the whole population (p < 0.0001) and after close contact (p < 0.0001), including
household contact \( (p < 0.0001) \), were significantly lower among individuals who had been vaccinated twice than among those who had not been vaccinated.

The RR of RT-PCR test positivity after contact with patients with COVID-19 (regardless of the contact level) in adults who had been vaccinated twice compared to adults who had never been vaccinated was 0.32 (95% CI 0.23–0.46). This result indicated that the COVID-19 vaccines were approximately 65%–70% (95% CI: 50%–80%) effective in preventing the transmission of the COVID-19 Delta variant. If we focus to the 567 individuals who had close (i.e., high-risk) contact history, the RR for acquiring the infection after a close contact after the second vaccine dose was 0.35 (95% CI: 0.24–0.50), which was almost the similar with the above result. Furthermore, the vaccine effectiveness after the first dose and before the second dose was estimated. The achieved RR was 0.61 (95% CI: 0.19–0.93), suggesting that only one vaccine dose was approximately 40%–45% (95% CI: 10%–80%) effective in preventing the transmission of the Delta variant. Lastly, because most of the not vaccinated participants were aged <65 years, RR was further calculated among the younger adult participants. The achieved RR after the second vaccine dose was 0.35 (95% CI: 0.22–0.56), and that after the first dose and before the second dose was 0.60 (95% CI: 0.39–0.94).

3.2. Effectiveness by time from vaccination

Next, to evaluate the changes in the effectiveness of vaccines to suppress the transmissibility according
to the passed time from receiving the second vaccine dose, RT-PCR test-positive rate among the participants who had contact with COVID-19 patients after having received the second vaccine dose by the passed time from vaccinations were calculated. The exact time periods from vaccinations to the RT-PCR swab test were available from 201 of the 240 individuals after the second vaccine dose (range: 1–138 days), and were divided into the following groups: 1–7 days (n=17), 8–30 day (n=55), 31–60 days (n=76), 61–90 days (n=38), and 91–140 days (n=15). The achieved test-positive rate and RR, when using the data in those who had not been vaccinated (n=472) as the reference group, are summarized in Table 2. The effectiveness of mRNA COVID-19 vaccines against the delta variant was suggested to be highest after 8–90 days from the second vaccine dose. The effectiveness against the delta variant may decrease after 90 days from the second vaccine dose compared to that of 8–90 days after the second dose (p=0.0533, Fisher exact test), but the sample size was too small to conclude this point.

3.3. Effectiveness of vaccines for the development of COVID-19 symptoms

As the distributions of age were significantly different between the groups based on the completion status of vaccines, the rate of symptomatic cases at the timing of the RT-PCR screening test among the RT-PCR test-positive cases were further evaluated in the younger adults aged <65 years and older adults aged ≥65 years. Among the older adults, the rate of symptomatic cases was 64.3% (n=9/14)
after second vaccine dose and 37.5% (n=3/8) without vaccinations (p=0.3777). Among the younger adults, the rate of symptomatic cases was 43.8% (n=7/16) after second vaccine dose and 81.3% (n=143/176) without vaccinations (p=0.0018). This result suggested that a completion of the second vaccine dose would significantly suppress the development of key COVID-19 symptoms after 3–7 days from a contact with patients among younger adults, with the calculated RR for developing symptoms after 3–7 days after a contact of 0.54 (95% CI: 0.31 – 0.94).

4. Discussion

The results of this study demonstrated that mRNA COVID-19 vaccines were effective both in suppressing the transmission and the development of COVID-19-related symptoms during the season of pandemic with the Delta variant. The obtained data showed that the two doses of vaccines prevented 50%–80% of the infection in the locality. The prevention rate after two doses of vaccines was larger than that after only one dose (i.e., 40%–45% effectiveness). Although this rate of effectiveness against the Delta variant may be slightly lower than that for the original strains, the vaccines significantly suppressed the transmission of COVID-19 in Japan, even during the pandemic season with the Delta variant. Furthermore, this study demonstrated that the development of key COVID-19 symptoms among the RT-PCR test-positive patients could be suppressed by the vaccines, especially in younger
age groups. The achieved data suggested that the vaccines were approximately 45%–50% effective for suppressing the development of COVID-19 symptoms at 3–7 days after contacting the patients. Another notable finding was that the rate of asymptomatic COVID-19 patients was slightly higher in older adults aged ≥65 years than in younger adults aged <65 years, regardless of the vaccine completion status. This fact may imply that asymptomatic infections may have played a significant role in maintaining and enhancing transmission not only in younger adults but also in older adults.

This study has several limitations. First, all enrolled individuals were of Asian ancestry. It is unclear whether the observed effectiveness can be generalized to Caucasians or African-Americans. Another limitation is that the number of individuals who underwent vaccination manufactured by the Moderna Corporation was small in this study. Further data may be needed to compare the effectiveness of the Moderna and Pfizer vaccines. Another limitation was that not all the participants were confirmed to be with the Delta variant by genome sequencing. During the study period, 0.5% -2% of the participants may have been infected by the strains other than the Delta variant. Lastly, this study evaluated the presence of key COVID-19 symptoms at 3–7 days after contacting the patients, but did not follow up the development of symptoms after the screening test. As median incubation period is estimated to be 5 days or longer after infection (Lauer et al. 2020; Qin et al. 2020), the data in this study regarding clinical manifestations may not outline the overall prevalence of key COVID-19 symptoms among the patients.
In conclusion, mRNA COVID-19 vaccines were effective in suppressing the transmission and also suppressing the development of key COVID-19 symptoms during the pandemic of the Delta variant in Japan. The mRNA vaccines prevented 50%–80% of the infection during the pandemic of the Delta variant in Japan.

Author contribution statement

TA, SK, and TI were involved in the conceptualization. All authors were involved in the data collection. TA, SK, MF, TN, and TI were involved in the data curation and the formal analysis. TA, SK, and TI were involved in the writing-original draft. All authors were involved in the writing-review & editing. SK, YK, K.Igarashi, SK, and TI supervised the process of this study. All authors meet the authorship and approved the final version of the manuscript.

Declaration of interests statement

There is no conflict of interests to be disclosed for this study.

Data availability statement

Anonymized data are available from the corresponding author upon reasonable requests from any
qualified researchers or clinicians.

Acknowledgements

The authors appreciate all medical staffs and local government staffs (Sendai City, Miyagi Prefecture) who joined and cooperated to the drive-through RT-PCR testing project. Also, the authors appreciate all participants to offer detailed clinical information that were essential to perform this study.

References


FIGURE LEGENDS

Fig. 1. Flow diagram for the study design

Among the individuals tested by nasopharyngeal nasal swab RT-PCR test at a single screening test center in Japan, the adults aged ≥18 years, who had a certain recent contact history with COVID-19 patients were enrolled in this study. They were further divided into those who were after the second vaccine dose, after the first dose and before the second dose, and not vaccinated. The transmissibility and the presence of self-reported COVID-19 symptoms were then compared between the groups.

COVID-19, coronavirus disease 2019; RT-PCR, reverse transcription-polymerase chain reaction; mRNA, messenger RNA; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Fig. 2. Ages by RT-PCR test results and vaccine completion status

Histograms for the age of participants in the total cohort (A), in the RT-PCR test-positive cases (B), in those after the second vaccine dose (C), and in those who had not been vaccinated (D) are depicted.

Rectangular boxes above the histograms show 25th and 75th percentiles, and vertical lines in the boxes show median.
Table 1. SARS-CoV-2 RT-PCR test positive rate according to completion of COVID-19 vaccination and contact situation

<table>
<thead>
<tr>
<th>Vaccinated (completed 2 doses)</th>
<th>Vaccinated (first dose only)</th>
<th>No vaccine</th>
<th>p-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>In total adult participants aged ≥ 18 years with recent contact history (n = 784)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT-PCR positive, n (%)</td>
<td>30/240 (12.5%)</td>
<td>17/72 (23.6%)</td>
<td>184/472 (39.0%)</td>
</tr>
<tr>
<td>BNT162b2 mRNA vaccine (Pfizer/BioNTech), n</td>
<td>20/161 (12.4%)</td>
<td>7/28 (25.0%)</td>
<td>same as above</td>
</tr>
<tr>
<td>mRNA-1273 vaccine (Moderna), n</td>
<td>4/36 (11.1%)</td>
<td>8/39 (20.5%)</td>
<td>same as above</td>
</tr>
<tr>
<td>Unknown manufactures, n</td>
<td>6/43 (14.0%)</td>
<td>2/5 (40.0%)</td>
<td>same as above</td>
</tr>
<tr>
<td>In the participants with CLOSE contact history (n = 567)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT-PCR positive, n (%)</td>
<td>27/166 (16.3%)</td>
<td>15/52 (28.8%)</td>
<td>164/349 (47.0%)</td>
</tr>
<tr>
<td>After a HOUSEHOLD contact (n = 311) *</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT-PCR positive, n (%)</td>
<td>17/98 (17.3%)</td>
<td>10/30 (33.3%)</td>
<td>89/183 (48.6%)</td>
</tr>
<tr>
<td>In the participants with LOW-RISK contact history (n = 217)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT-PCR positive, n (%)</td>
<td>3/74 (4.1%)</td>
<td>2/20 (10.0%)</td>
<td>20/123 (16.3%)</td>
</tr>
<tr>
<td>In older adults aged ≥ 65 years (n = 156)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT-PCR positive, n (%)</td>
<td>14/124 (11.3%)</td>
<td>1/5 (20.0%)</td>
<td>8/27 (29.6%)</td>
</tr>
<tr>
<td>In younger adults aged 18-65 years (n = 628)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT-PCR positive, n (%)</td>
<td>16/116 (13.8%)</td>
<td>16/67 (23.9%)</td>
<td>176/445 (39.6%)</td>
</tr>
</tbody>
</table>

The p-values are the results of the chi-square test or Fisher’s exact test between the participants who had been completely vaccinated (the second column) and those who have never been vaccinated (fourth column).

* All 311 cases with household contact were included in the 427 cases with close contact.
Table 2. RT-PCR test-positive rate after a contact episode by the passed time from the second vaccine dose

<table>
<thead>
<tr>
<th>Time periods *</th>
<th>RT-PCR test-positive : negative, n</th>
<th>RT-PCR test-positive rate, % (95% CI)</th>
<th>p-value †</th>
<th>RR (95% CI) ‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–7 days</td>
<td>6 : 11</td>
<td>35.3% (17.3–58.7)</td>
<td>0.8067</td>
<td>0.91 (0.47–1.74)</td>
</tr>
<tr>
<td>8–30 days</td>
<td>7 : 48</td>
<td>12.7% (6.3–24.0)</td>
<td>&lt; 0.0001</td>
<td>0.33 (0.16–0.66)</td>
</tr>
<tr>
<td>31–60 days</td>
<td>6 : 70</td>
<td>7.9% (3.7–16.2)</td>
<td>&lt; 0.0001</td>
<td>0.20 (0.09–0.44)</td>
</tr>
<tr>
<td>61–90 days</td>
<td>2 : 36</td>
<td>5.3% (1.5–17.3)</td>
<td>&lt; 0.0001</td>
<td>0.14 (0.03–0.52)</td>
</tr>
<tr>
<td>91–140 days</td>
<td>4 : 11</td>
<td>26.7% (10.9–52.0)</td>
<td>0.4254</td>
<td>0.68 (0.29–1.60)</td>
</tr>
</tbody>
</table>

CI, confidence interval; RR, risk ratio; RT-PCR, reverse transcription-polymerase chain reaction

* Time periods were divided according to the days from the second vaccine dose to the RT-PCR swab test.

† The p-values are the results of Fisher exact test by using the 472 tested individuals who had not been vaccinated as the reference group.

‡ The risk ratios were also calculated by using the 472 not vaccinated individuals as the reference group.
SARS-CoV-2 RT-PCR tested individuals at a testing center from August to September 2021 (n=2219) (During the period of pandemic with **Delta variant** in Japan)

excluded  Individuals **without a certain contact history** with COVID-19 patients (n=312)

RT-PCR tested individuals with a certain contact history (n=1907) [High-risk contact (n=1103) Low-risk contact (n=804)]

excluded  **Non-adults** aged <18 years (n=1123)

**Eligible:** Adults aged ≥18 years with a contact history (n=784) [High-risk contact (n=567) Low-risk contact (n=217)]

Completion status of mRNA COVID-19 vaccines

- Post-second vaccine dose (n=240)
- Post-first dose, no second dose (n=72)
- Not vaccinated (n=472)
(A) Whole participants (n = 784)

(B) RT-PCR test-positive cases (n = 231)

(C) After the second vaccine dose (n = 240)

(D) Not vaccinated (n = 472)