

A low proportion of asymptomatic COVID-19 patients with the Delta variant infection by viral transmission through household contact at the time of confirmation in Ibaraki, Japan

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Abstract: We conducted a study to investigate the proportion of patients with asymptomatic coronavirus disease 2019 (COVID-19) infected with the Delta variant compared with those infected with the wild-type strain at the time of confirmation. A total of 504 patients with confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection by viral transmission through household contact in Ibaraki, Japan were included. The proportion of asymptomatic COVID-19 patients at the time of confirmation was compared between patients infected with L452R mutation strain from June to September 2021 and those infected with the wild-type strain from November 2020 to January 2021, and was found to be 14.2% and 28.8%, respectively (relative risk, 0.49; 95% confidence interval, 0.35-0.70). The proportion of asymptomatic COVID-19 patients by viral transmission through household contact was lower among the Delta variant than those among the wild-type strain at the time of confirmation. It might contribute to attenuation of transmission.

Keywords: Delta variant, coronavirus disease 2019 (COVID-19), asymptomatic, Japan

Introduction

The Delta variant (also known as Pango B. 1.617.2 strain) is a lineage of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and was classified as a variant of concern (VOC) on May 11, 2021 (1). The estimated transmissibility of this variant is increased by 97% (2). VOCs bearing the L452R spike protein mutation demonstrated increased transmissibility, infectivity, and evasion of antibody neutralization (3). The Delta variant has been reported from 191 countries across all six World Health Organization regions and has become the dominant strain in many countries (4).

In Japan, as of November 2021, a surge of novel coronavirus disease 2019 (COVID-19) occurred five times, and a total of 1.7 million patients with COVID-19 were reported. The third wave with the wild-type strain peaked in January 2021, and the fourth wave with the Alpha variant dominance peaked in May 2021 (5).

Patients infected with the Delta variant *via* domestic transmission began to be confirmed in the latter half of May. The fifth wave of COVID-19, which was primarily caused by the Delta variant, occurred from the latter half of July 2021 to August 2021, with a daily

reported number of patients ranging from 3,408 on July 15 to 25,858, the peak, on August 20. The proportion of SARS-CoV-2 virus strain with L452R mutation, which almost corresponded to the Delta variant in Japan, was 89% in the week from August 16 to August 22. However, the daily reported number of patients decreased rapidly after September, and was 17,702 on August 31, 1,568 on September 30, and 147 on October 25 (6,7). Although the development of vaccines and social interventions during July-August might have contributed to the decline in the number of patients, the cause of the rapid decline in the number of patients in the fifth wave in Japan has not been completely elucidated.

SARS-CoV-2 can be transmitted through contact with asymptomatic or pre-symptomatic individuals (8). A high proportion of asymptomatic patients may make the control of the COVID-19 outbreak difficult (9). However, the Delta variant may reduce the proportion of asymptomatic patients (10,11). One possible reason behind the rapid decline in the number of COVID-19 patients may be the decline in the proportion of asymptomatic or pre-symptomatic patients in the community, decreasing the undiscovered transmission sources. To the best of our knowledge, no reviewed study reported the proportion of asymptomatic COVID-19

patients among those infected with the Delta variant in Japan.

This study aimed to investigate the proportion of patients with asymptomatic COVID-19 infected with the Delta variant compared to those infected with the wild-type strain at the time of confirmation.

Study 1 on household transmission in southeastern Ibaraki

In this study, a cross-sectional study design was employed.

Study 1 was carried out in the southeastern area of Ibaraki, the jurisdiction of the Itako Public Health Center, and the Tsuchiura Public Health Center of the Ibaraki Prefectural Government in Japan. The area is located about 90 km east-northeast of Tokyo and has a population of 520,000.

In Ibaraki, no patients infected with a VOC were detected until February 2021. The first patient infected with N501Y mutation and L452R variant was detected in the twelfth week (March 22–28) and the twenty-fifth week (June 21–27), respectively. The proportion of patients infected with the L452R mutation strain was 53% in the week from July 19 to July 25, and 82% from August 9 to August 15 (12). The L452R mutation is also observed in other variants of interest, such as the Kappa variant. However, almost all patients infected with the L452R mutation strain in Japan were confirmed to be infected with the Delta variant on investigating RNA sequencing (6,7).

No patients were vaccinated against COVID-19 in Ibaraki until January 2021. The proportion of patients who were vaccinated twice was 85% for those aged ≥ 70 years, according to the data released on August 16. In contrast, it was $< 20\%$ for those aged < 60 years (13).

The eligible participants were patients with confirmed COVID-19, who were assumed to be infected through contact with another household patient with COVID-19 as defined by the Public Health Center. The procedure for participant involvement and data collection has been described in a previous study (14).

Participants during the wild-type strain dominant period included patients with confirmed COVID-19 between November 2020 and January 2021. Only a small number of patients had been reported during the first wave and the second wave, until October 2020, in the area. The number of patients increased during the third wave, from November 2020 to January 2021, in the area. B.1.1.214 strain was dominant among wild strains during the period in Japan (15). Patients infected with the Delta variant during June–September 2021, who had an L452R mutation detected in their specimen or the specimen of their contacts, were included. The first Delta variant was detected in June in Ibaraki (12). The Delta variant dominant fifth wave was observed from July to September though patients with Alpha

variant constituted part of the patients at the beginning of the fifth wave (7).

In Japan, according to the Infectious Diseases Control Law (The Law), the public health center is notified of all COVID-19 cases (16). SARS-CoV-2 infections were confirmed using polymerase chain reaction (PCR) test with a cycle threshold value of 40, loop-mediated isothermal amplification test, antigen quantitative test, or monoclonal antigen qualitative test.

The public health center collected patient' data on demographics, symptoms, and history of vaccination based on this law.

We compared the proportion of asymptomatic patients by age group in the Delta variant dominant period with that in the wild-type strain dominant period. Relative risks were calculated using 95% confidence intervals (CI). In study 1, mean diagnostic delay for symptomatic patients was calculated for patients with the L452 mutation and with the wild-type strain. Statistical analyses were performed using R software, version 4.1-1 (R Foundation for Statistical Computing, Vienna, Austria).

The study protocol was approved on July 8, 2021, by the Ibaraki Prefecture Epidemiological Research Joint Ethics Review Committee (protocol number: R3-1). The study was implemented following the law and exempted from obtaining informed consent under "the ethical guidelines for life science and medical research on human subject" in Japan.

Study 2 on both household and non-household transmission in the entire Ibaraki

In study 2, we aimed to confirm findings in Study 1 to be applied in the entire Ibaraki as sensitive analyses, and to externally validate the results among non-household contacts.

In study 2, the entire Ibaraki prefecture, with a population of 2,840,000, was included. Patients with confirmed COVID-19 infection by known contact, both household and non-household, were included. We retrieved publicly available data disclosed on the official website of the Ibaraki prefectural government. The data included the date of onset of symptoms before disclosure but did not include information on L452R mutation detection. Participants during the wild-type strain dominant period included patients with confirmed COVID-19 between November 2020 and January 2021. Participants during the Delta variant dominant period included patients with confirmed COVID-19 in August 2021, regardless of the L452R mutation detection test result.

We compared the proportion of asymptomatic patients by age group in the Delta variant dominant period with that in the wild-type strain dominant period. Relative risks were calculated using 95% confidence intervals (CI).

Low proportion of asymptomatic COVID-19 patients among the Delta variant

In Study 1, the proportion of patients with asymptomatic COVID-19 infected *via* household transmission was 14.2% (41 out of 289) for patients with L452R mutation strain during June-September 2021 compared with 28.8% (62 out of 215) for patients with the wild-type strain during November 2020–January 2021 (relative risk, 0.49; 95% CI, 0.35-0.70). Among patients aged 20-59 years, the proportion of asymptomatic patients was 8.5% for patients infected with L452R mutation strain compared to 24.3% for patients with the wild-type strain (relative risk, 0.35; 95% CI, 0.18-0.66) (Table 1). Among unvaccinated patients, asymptomatic patients were 23 out of 102 (22.5%) aged 0-19 years, 7 out of 105 (6.7%) aged 20-59 years, and 4 out of 20 (20%) aged 60 years. Three out of 24 (12.5%) partially vaccinated patients were asymptomatic and 4 out of 28 (14.3%) completely vaccinated (≥ 2 weeks following the second vaccination) patients were asymptomatic.

Mean diagnostic delay was 2.57 days for infection with L452R mutation strain, and 3.61 days for patients with the wild-type strain.

In the entire Ibaraki in Study 2, the proportion of patients with asymptomatic COVID-19 infection by known contact was 13.7% during August 2021 compared to 30.3% during November 2020–January 2021 (relative risk, 0.45; 95% CI, 0.42-0.50). Among patients aged 20-59 years, the proportion of patients with asymptomatic COVID-19 was 10.6% in August 2021 compared to 28.1% during November 2020–

January 2021 (relative risk, 0.38; 95% CI, 0.33-0.43) (Table 2). The proportion of patients with asymptomatic COVID-19 infected by unknown contact were 4.6% of 2,542 patients between November 2020 and January 2021 and 3.8% of 3,316 patients in August 2021.

Possible implications of findings

The proportion of patients with asymptomatic COVID-19 at the time of confirmation was lower among those infected with the Delta variant than those infected with the wild-type strain, both in household contacts, despite shorter diagnostic delay, in the southeastern part of Ibaraki (Study 1), and in contact with the whole Ibaraki (Study 2). The proportion was low, especially in the age group 20-59 years.

Several studies have reported a decline in the proportion of patients with asymptomatic COVID-19 and early onset of symptoms after exposure to the Delta variants (9-11). Our results are consistent with those in the literature.

Asymptomatic patients at the time of confirmation included both asymptomatic and pre-symptomatic patients. Symptomatic patients may be quarantined voluntarily or after confirmation of infection by visiting physicians, albeit asymptomatic or pre-symptomatic patients remain unaware of the infection and continue viral shedding in the community. Although pre-symptomatic patients later become symptomatic and may be isolated, most of the transmission to other contacts occurs either in the pre-symptomatic period or a few days after onset of symptoms (11). Therefore, a decrease

Table 1. The proportion of patients with asymptomatic COVID-19 at the time of confirmation infected *via* household transmission in the southeastern part of Ibaraki

Period	June–September 2021		November 2020–January 2021		Relative risk (95% confidence interval)
Mutation test	L452R mutation		No		
Age (years)	Patients <i>n</i>	Asymptomatic* <i>n</i> (%)	Patients <i>n</i>	Asymptomatic* <i>n</i> (%)	
0 - 19	103	23 (22.3)	45	12 (26.7)	0.84 (0.46-1.53)
20 - 59	142	12 (8.5)	103	25 (24.3)	0.35 (0.18-0.66)
60	44	6 (13.6)	67	25 (37.3)	0.37 (0.16-0.82)
Total	289	41 (14.2)	215	62 (28.8)	0.49 (0.35-0.70)

*Asymptomatic at the time of confirmation.

Table 2. The proportion of patients with asymptomatic COVID-19 infected by known contact in the whole of Ibaraki

Period	August 2021		November 2020–January 2021		Relative risk (95% confidence interval)
Age (years)	Patients <i>n</i>	Asymptomatic* <i>n</i> (%)	Patients <i>n</i>	Asymptomatic* <i>n</i> (%)	
0 - 19	1,452	253 (17.4)	416	139 (33.4)	0.52 (0.44-0.62)
20 - 59	3,099	327 (10.6)	1,522	427 (28.1)	0.38 (0.33-0.43)
20 - 39	1,806	189 (10.5)	758	220 (29.0)	0.36 (0.30-0.43)
40 - 59	1,293	138 (10.7)	764	207 (27.1)	0.39 (0.32-0.48)
60 -	496	111 (22.4)	604	204 (33.8)	0.66 (0.54-0.81)
60 - 79	403	85 (21.1)	422	136 (32.2)	0.65 (0.52-0.83)
80 -	93	26 (28.0)	182	68 (37.4)	0.75 (0.51-1.09)
Total	5,055	696 (13.7)	2,542	770 (30.3)	0.45 (0.42-0.50)

*Asymptomatic at the time of disclosure.

in the proportion of patients with asymptomatic or pre-symptomatic COVID-19 may contribute to a decrease in the number of infected patients in the next generation in the community (9,17).

The reason behind the rapid decrease in the number of patients with COVID-19 from September to October 2021 in Japan has not been sufficiently elucidated. In Ibaraki, since the Delta variant became predominant from mid-July, the number of patients with COVID-19 increased rapidly, resulting in the fifth wave. If this increase influenced symptomatic patients to quarantine themselves or visit physicians since August, the subsequent decrease in the proportion of unconscious or undiscovered sources of transmission combined with other factors, such as rapid development of vaccination in August-September 2021, might have contributed to the rapid attenuation of virus transmission.

Several months after vaccination, the preventive effect on infection may decrease among vaccinated persons, breakthrough infections may increase, and the proportion of patients with asymptomatic or pre-symptomatic COVID-19 may increase again (10,18). The number of infected patients with Delta variant increased again at the end of 2021 in Japan; it was replaced with Omicron variant in January, 2022. It is necessary to continue protective measures, such as wearing masks and ventilation and implementing booster vaccination.

This study had several limitations. First, this study employed a cross-sectional design; thus, the results did not show any causal relationships. Second, in Study 1, we defined patients with the earliest onset date as the index patients in a household without any patients with COVID-19 with apparent exposure to SARS-CoV-2. The index patients might have been misclassified as secondary patients. Third, the data in Study 2 were collected only through websites and their authenticity could not be confirmed.

Further studies on the Delta variant regarding its transmission dynamics and prediction using mathematical models are warranted.

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