Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.7033-21
Intern Med 60: 2569-2575, 2021
http://internmed.jp

【 ORIGINAL ARTICLE 】

# SARS-CoV-2 Infection among Medical Institution Faculty and Healthcare Workers in Tokyo, Japan

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**Abstract:**

**Objective** To consider effective measures against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in medical institutions, this study estimated the SARS-CoV-2 infection rate among healthcare workers (HCWs) in Tokyo, Japan, and determined the specific findings for mild coronavirus disease 2019 (COVID-19) cases.

**Methods** This study analyzed the results of serologic tests to detect immunoglobulin G antibodies against SARS-CoV-2 and evaluated the demographic and clinical characteristics of the faculty and HCWs at a Tokyo medical institution in August 2020. The demographic and clinical characteristics of participants with antibody-positive results were compared to those of participants with antibody-negative results.

**Materials** This study recruited 2,341 faculty and HCWs at a Tokyo medical institution, 21 of whom had a COVID-19 history.

**Results** Of the 2,320 participants without a COVID-19 history, 20 (0.862%) had positive serologic test results. A fever and dysgeusia or dysosmia occurred with greater frequency among the participants with positive test results than in those with negative results [odds ratio (OR), 5.475; 95% confidence interval (CI), 1.960-15.293 and OR, 24.158; 95% CI, 2.693-216.720, respectively]. No significant difference was observed in the positivity rate between HCWs providing medical care for COVID-19 patients using adequate protection and other HCWs (OR, 2.514; 95% CI, 0.959-6.588).

**Conclusion** To reduce the risk of COVID-19 spread in medical institutions, faculty and HCWs should follow standard and necessary transmission-based precautions, and those with a fever and dysgeusia or dysosmia should excuse themselves from work as soon as possible.

**Key words:** SARS-CoV-2, COVID-19, healthcare worker

**(Intern Med 60: 2569-2575, 2021)**
**(DOI: 10.2169/internalmedicine.7033-21)**

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Received: January 4, 2021; Accepted: May 13, 2021; Advance Publication by J-STAGE: June 19, 2021
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## Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection caused an outbreak of coronavirus disease 2019 (COVID-19) that first occurred in December 2019 in Wuhan, China, and subsequently became disseminated globally. As of July 31, 2020, 17,106,007 people have been infected, and 668,910 people have died of COVID-19 (1). Now beyond all control, COVID-19 is currently the most serious public health crisis in the world. In Japan, however, the total numbers of cases and deaths is only 34,372 and 1,006, respectively (1), which are relatively low numbers among developed countries.

Medical institutions are at high risk for COVID-19 outbreaks because patients with COVID-19 may seek care there, and these institutions also serve many patients who are immunocompromised as well as older patients, both populations that may be particularly susceptible to SARS-CoV-2 infection and the contraction of COVID-19 (2). Indeed, at the authors' medical institution in Tokyo, Japan, nosocomial outbreaks of COVID-19 have occurred (3), defined as infections associated with SARS-CoV-2 transmission between healthcare workers (HCWs) and patients.

SARS-CoV-2-infected individuals are more likely to be contagious in earlier stages of the illness than in later stages. A retrospective study among 77 transmission pairs in China, showed that infectiousness started 2.3 days before the symptom onset, peaked at 0.7 days before the symptom onset, and declined within 7 days of the symptom onset (4). A prospective study among 2,761 close contacts of 100 patients with COVID-19 in Taiwan showed that all 22 secondary cases had their first exposure to the index case within 6 days of the symptom onset (5). The hypothesis for this current study is that the risk of COVID-19 spread may be reduced not only by using standard contact and droplet precautions but also by the early detection and isolation of suspected COVID-19 patients.

The Chinese Center for Disease Control and Prevention reported that the number of mild cases was 36,160 (80.9%) among 44,762 patients with confirmed COVID-19 infection (6). In a COVID-19 outbreak on cruise ship quarantined in Yokohama, Japan, 544 individuals (20.4%) were infected with SARS-CoV-2 among 2,666 passengers (7). It is interesting to note that 190 (34.9%) of these cases were mild, and 314 (57.7%) were asymptomatic. In another outbreak in February 2020 when the COVID-19 lockdown started in Italy, a survey of the resident population of the town of Vo' was conducted to investigate the exposure to SARS-CoV-2. Polymerase chain reaction (PCR) test results were positive for SARS-CoV-2 in 73 of 2,812 individuals (8). Among the 73 residents with positive tests, 29 (39.7%) were asymptomatic. These reports from China, Japan, and Italy suggest that many cases of SARS-CoV-2 infection are mild or asymptomatic. Therefore, many more individuals may be infected with SARS-CoV-2 than are confirmed by the SARS-CoV-2 PCR test, as an individual with mild symptoms may believe there is little need to undergo testing or may not be directed to receive a test by their primary care provider.

In addition, the sensitivity of PCR tests with nasopharyngeal swabs has been reported to be around 70-80% (9, 10), and some cases of infection may not be diagnosed even if tested. Therefore, it is typically difficult to accurately estimate the SARS-CoV-2 infection rate in a population; however, an estimation of the infection rate is necessary to support COVID-19 countermeasures. Although the SARS-CoV-2 PCR test can only detect current infection, the serum antibody against SARS-CoV-2 test can detect a history of infection.

The present study considered effective measures against SARS-CoV-2 infection in medical institutions. The serum antibody test was used to estimate the SARS-CoV-2 infection rate among faculty and HCWs at a medical institution in Tokyo, Japan. In addition, the characteristics between study participants with antibody positivity and those with antibody negativity were compared to reveal specific findings for mild cases of COVID-19 infection.

## Materials and Methods

### *Study population and study design*

Keio University comprises a medical school and a 1,000-bed university hospital in Tokyo, Japan. This single-center, retrospective study was conducted in August 2020 to analyze the results of serologic tests to detect immunoglobulin G (IgG) antibodies to SARS-CoV-2 and evaluate the medical information for faculty of Keio University School of Medicine and HCWs of Keio University Hospital, all of whom gave their informed consent.

This study was conducted in compliance with the Declaration of Helsinki and was approved by the Institutional Ethics Review Committee for Human Research at Keio University School of Medicine and Keio University Hospital.

### *Measurement of serum IgG antibody titers against SARS-CoV-2*

Serum IgG antibody titers against SARS-CoV-2 were measured using the iFlash-SARS-CoV-2 (Yhlo Biotech, Shenzhen, China), a paramagnetic particle chemiluminescent immunoassay (CLIA) for the identification of IgG antibodies against SARS-CoV-2 nucleocapsid protein and spike protein. According to the manufacturer's instructions, the assay was considered positive when the IgG was ≥10 AU/mL. If the participant tested positive for IgG antibodies, a SARS-CoV-2 PCR test was performed to confirm whether they had a current or history of infection.

### *Collection of medical information*

To determine the characteristics of individuals infected with SARS-CoV-2, the study obtained information on the participant sex, age, and profession. In addition, structured

**Table 1. Demographic Characteristics of Study Participants.**

| | | Subjects (n=2,320) | IgG antibody positive (n=20) | (%) | OR | 95%CI |
|---|---|---|---|---|---|---|
| Sex | | | | | | |
| | Female | 1,491 | 7 | 0.469 | Reference | |
| | Male | 829 | 13 | 1.568 | 3.377 | 1.342-8.499 |
| Age | years | | | | | |
| | 20-29 | 614 | 6 | 0.977 | Reference | |
| | 30-39 | 673 | 7 | 1.040 | 1.065 | 0.356-3.187 |
| | 40-49 | 547 | 3 | 0.548 | 0.559 | 0.139-2.245 |
| | 50-66 | 486 | 4 | 0.823 | 0.841 | 0.236-2.997 |
| Profession | | | | | | |
| | Nurses | 752 | 4 | 0.532 | Reference | |
| | Medical doctors | 564 | 7 | 1.241 | 2.350 | 0.685-8.067 |
| | Technicians | 416 | 2 | 0.481 | 0.903 | 0.165-4.953 |
| | Researchers | 303 | 3 | 0.990 | 1.870 | 0.416-8.405 |
| | Medical processors | 285 | 4 | 1.404 | 2.662 | 0.661-10.716 |

CI: confidence interval, IgG: immunoglobulin G, OR: odds ratio

questionnaires and medical records were used to determine if the following factors were present for participants from January to August 2020: symptoms of acute respiratory illness; dysgeusia or dysosmia; a fever (≥37.5 °C); other symptoms, such as fatigue and abdominal pain; close contact with COVID-19 patients; and provision of medical care for COVID-19 patients under adequate protection. "Close contact" was defined as providing direct care for COVID-19 patients without appropriate personal protective equipment (PPE) or being within 1 m of a COVID-19 patient for ≥15 minutes without appropriate PPE from 2 days before the symptom onset until the time when the patient was isolated. For participants with a history of COVID-19, the time interval between the symptom onset or diagnosis and SARS-CoV-2 PCR-negative conversion was also obtained from medical records.

### Statistical analyses

Comparisons of the study participant characteristics and test results were analyzed to determine significant differences using Fisher's exact test or an unpaired *t*-test. The proportional odds ratios (ORs) were calculated to compare the risk of SARS-CoV-2 infection for each group to that of a specific group as a reference. Statistical analyses of the data were performed using the SPSS, version 25 (IBM, Armonk, USA) and R software programs (The R Foundation, Vienna, Austria).

## Results

In August 2020, 3,304 faculty members of the medical school and HCWs of the university hospital received an annual health checkup. Titers of serum IgG antibody against SARS-CoV-2 were measured for the 2,341 faculty and HCWs who agreed to participate in the study. Among the 2,341 participants, 21 had a history of COVID-19 infection. Among the remaining 2,320 participants without a COVID-19 history, 20 [0.862%; 95% confidence interval (CI), 0.527%-1.328%] had positive results. Table 1 shows the results of the serum IgG antibody test categorized by participant sex, age, and professions. Although no significant difference in the positive rate was observed between the groups categorized by age and profession, the positive rate differed by sex, showing a significantly higher rate for men than women (1.568% vs. 0.469%). All 20 participants with positive results for the serum IgG antibody test had negative results for the SARS-CoV-2 PCR test, indicating that they had a history of infection.

The study then compared the characteristics of the 20 participants with positive serum IgG antibody test results and the 2,300 participants with negative results (Table 2). More participants with positive results had a history of any symptoms than did those with negative results [10 (50.000%) vs. 374 (16.261%)], while the median (interquartile range) intervals between the symptom onset and serologic test were 5 months (4-5 months) and 5 months (2-6 months) among the participants with positive and negative results, respectively. Specifically, a fever (≥37.5 °C) and dysgeusia or dysosmia occurred with greater frequency among the participants with positive results than among those with negative results (OR, 5.475; 95% CI, 1.960-15.293 and OR, 24.158; 95% CI, 2.693-216.720, respectively). In contrast, 10 (0.519%, 95% CI 0.249%-0.953%) participants had antibody-positive results among the 1,926 without a history of any symptoms. Although the participants who were close contacts of a COVID-19 patient tended to have positive results (OR, 6.796; 95% CI, 1.522-30.352), no significant difference was observed in the positive rate between the participants providing medical care to COVID-19 patients using adequate protection and other participants (OR, 2.514; 95% CI, 0.959-6.588).

Of the 21 participants with a history of COVID-19, 7

**Table 2. Clinical Characteristics of Study Participants**

| | | IgG antibody negative (n=2,300) | (%) | IgG antibody positive (n=20) | (%) | OR | 95%CI |
|---|---|---|---|---|---|---|---|
| **Symptom** | | | | | | | |
| Had one or more symptoms | No | 1,926 | 83.739 | 10 | 50.000 | Reference | |
| | Yes | 374 | 16.261 | 10 | 50.000 | 5.150 | 2.129-12.459 |
| Had symptoms of acute respiratory illness | No | 2,034 | 88.435 | 15 | 75.000 | Reference | |
| | Yes | 266 | 11.565 | 5 | 25.000 | 2.549 | 0.919-7.070 |
| Had dysgeusia or dysosmia | No | 2,295 | 99.783 | 19 | 95.000 | Reference | |
| | Yes | 5 | 0.217 | 1 | 5.000 | 24.158 | 2.693-216.720 |
| Had fever (≥37.5°C) | No | 2,168 | 94.261 | 15 | 75.000 | Reference | |
| | Yes | 132 | 5.739 | 5 | 25.000 | 5.475 | 1.960-15.293 |
| Had other symptoms | No | 2,198 | 95.565 | 18 | 90.000 | Reference | |
| | Yes | 102 | 4.435 | 2 | 10.000 | 2.394 | 0.548-10.458 |
| **Contact with COVID-19 patients** | | | | | | | |
| Had close contact | No | 2,263 | 98.391 | 18 | 90.000 | Reference | |
| | Yes | 37 | 1.609 | 2 | 10.000 | 6.796 | 1.522-30.352 |
| Provided medical care under adequate protection | No | 1,965 | 85.435 | 14 | 70.000 | Reference | |
| | Yes | 335 | 14.565 | 6 | 30.000 | 2.514 | 0.959-6.588 |

CI: confidence interval, COVID-19: coronavirus disease 2019, IgG: immunoglobulin G, OR: odds ratio

**Table 3. Demographic Characteristics of Study Participants with a COVID-19 History**

| | | Subjects (n=21) | IgG antibody positive (n=7) | (%) | OR | 95%CI |
|---|---|---|---|---|---|---|
| Sex | | | | | | |
| | Female | 13 | 3 | 23.077 | Reference | |
| | Male | 8 | 4 | 50.000 | 3.333 | 0.502-22.142 |
| Profession | | | | | | |
| | Nurses | 9 | 4 | 44.444 | Reference | |
| | Medical doctors | 7 | 2 | 28.571 | 0.500 | 0.061-4.091 |
| | Technicians | 4 | 0 | 0.000 | - | - |
| | Researchers | 0 | 0 | 0.000 | - | - |
| | Medical processors | 1 | 1 | 100.000 | - | - |

CI: confidence interval, COVID-19: coronavirus disease 2019, IgG: immunoglobulin G, OR: odds ratio

were IgG antibody-positive, and no significant differences were observed in the sex, age, or profession between these 7 participants with positive results and the 14 with negative results (Table 3, Figure A). However, the time interval between the symptom onset or diagnosis and SARS-CoV-2 PCR-negative conversion was significantly longer for participants with positive results than for those with negative results, as indicated by the mean±standard deviation (SD) (17.000±4.000 days vs. 7.714±2.268 days, $p<0.001$; Figure B).

## Discussion

Thus far, information on COVID-19 has been insufficient to prevent its worldwide spread because it is an emerging infectious disease. Furthermore, many cases among individuals infected with SARS-CoV-2 present with either no symptoms or mild symptoms, which makes it difficult to accurately determine the SARS-CoV-2 infection status in a population. In the present study, the results of the serum IgG antibody against SARS-CoV-2 test for the 2,320 faculty and HCWs at a Tokyo medical institution showed an antibody prevalence rate of 0.862%. In Tokyo, with a population of 14 million, the number of cumulative cases with PCR-positive results from January to July 2020 was 12,691 (11). These findings suggests that many mild cases or asymptomatic cases exist among those who were infected with SARS-CoV-2 but not diagnosed. In addition, a history of a fever and dysgeusia or dysosmia was more frequent among the study participants with positive results than those with negative results, suggesting that these symptoms may be the most important findings suggestive of mild COVID-19 infection.

Few reports have addressed the antibody prevalence among HCWs in Japan. In May 2020, the Anti-SARS-CoV-2 Antibody Testing Equipment User Council conducted a research survey of antibody prevalence rate among 1,000 outpatients of medical institutions using the iFlash-SARS-CoV-

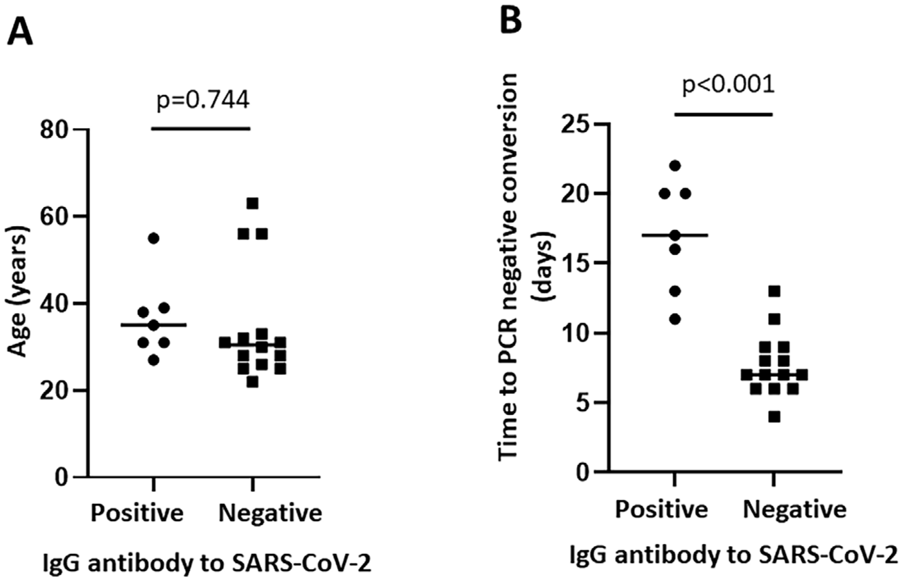


**Figure. The comparisons of the (A) age and (B) time interval between the symptom onset or diagnosis and severe infection with acute respiratory syndrome coronavirus 2 (SARS-CoV-2) polymerase chain reaction (PCR)-negative conversion (time to PCR-negative conversion) between participants with a history of coronavirus disease 2019 (COVID-19) who had immunoglobulin G (IgG) antibody-positive results (positive, n=7) and antibody-negative results (negative, n=14). Data are shown as scattergrams with horizontal lines in each group. Comparisons between two groups were assessed using an unpaired t-test.**

2, the same antibody test as used in the present study (12). This previous study reported an antibody prevalence rate of 0.70%, which was not significantly different from that in the present study (p=0.833). In June 2020, a research survey conducted by the Ministry of Health, Labour and Welfare of Japan concerning the antibody prevalence rate among 1,971 persons living in Tokyo reported a rate of 0.10%, which was significantly lower than that of the present study (p< 0.001) (13). Many antibody tests are currently available, but the accuracy of those tests varies widely (14). The study by the Ministry of Health, Labour and Welfare of Japan used an antibody test produced by Roche Diagnostics and Abbott, which was different from that used in the present study and may have been the cause of the significant difference in the prevalence rates between the two studies. In addition, the study by the Ministry of Health, Labour and Welfare of Japan among the general public, who have a lower risk of exposure to SARS-CoV-2 than HCWs, was conducted before the “second wave” of the epidemic in Japan. These points may have resulted in the antibody prevalence rate being lower for that study than in the present study.

A number of reports have investigated the antibody prevalence rate among HCWs in foreign countries (15, 16). In March and April 2020, the antibody prevalence rate was 7.6% among 578 HCWs in Spain (15). From April to June 2020, the antibody prevalence rate was 6.0% among 3,248 HCWs in United States (16). The antibody prevalence rate in the present study was markedly lower than the rates in previous studies; however, the study periods and antibody tests differed among studies, which may have caused this discrepancy. The World Health Organization reported that the number of confirmed COVID-19 cases in the United States and Europe was markedly higher than that of Japan (1), so differences in the overall situation among different national COVID-19 epidemics may also have influenced the significant differences in the antibody prevalence rate for HCWs.

Regarding sex differences, men with COVID-19 infection experienced more severe disease and higher mortality than women (17, 18). Although differences in the values of angiotensin-converting enzyme 2, immune function, and sex hormones between the sexes may be associated with disease severity and mortality, the specific reasons remains unclear (19). In the present study, the antibody prevalence rate for men was significantly higher than that for women, suggesting that susceptibility to SARS-CoV-2 for men is higher than that for women.

In the present study, the participants with IgG antibody positivity tended to have a history of any symptoms, especially a fever and dysgeusia or dysosmia, compared with those with IgG antibody negativity. An antibody prevalence study of 2,149 HCWs in Sweden reported that the symptoms significantly associated with IgG antibody positivity were a fever, ageusia, and anosmia (20). To reduce the risk of COVID-19 spread in medical institutions, faculty or HCWs with these symptoms should excuse themselves from work as soon as possible. However, it is important to note that the IgG antibody prevalence rate was 0.519% among the participants without a history of any symptoms, suggesting the existence of asymptomatic carriers who have the potential to transmit the virus to others (21, 22).

The IgG antibody prevalence rate of HCWs providing medical care for COVID-19 patients using adequate protection was not significantly higher than that of the other participants. Based on these results, the risk of SARS-CoV-2 infection is considered comparable to that of HCWs not caring for COVID-19 patients, provided that standard precautions - and, if necessary, transmission-based precautions - are taken when caring for patients with COVID-19.

Although the anti-SARS-CoV-2 antibody test is currently used for the estimation of the SARS-CoV-2 infection rate in a population (23, 24), a few reports have indicated that after the acute phase of infection, the antibody titers degrade over time (25, 26). In a study comparing the antibody titers in individuals with infection in the acute phase to those in the convalescent phase among 30 asymptomatic cases and 31 symptomatic cases, the antibody titers declined in 28 cases (93.3%) and 30 cases (96.8%), respectively (25). The IgG antibody titers of 31 mild cases with COVID-19 were serially measured, and their half-life was 26-60 days (26). In addition, the present study showed that, among participants with a COVID-19 history, the IgG-positive participants had a longer period from the symptom onset or diagnosis to negative conversion on a PCR test than did the IgG-negative participants. Based on the present and previous findings, it may be difficult to identify individuals who either had a long-term recovery and were cured of a previous COVID-19 infection or whose SARS-CoV-2 titer was eliminated in a relatively short period of time and then accurately estimate the SARS-CoV-2 infection rate using an antibody test. Therefore, the antibody prevalence rate may have been underestimated in the present study.

Several limitations associated with the present study warrant mention. Although the number of study participants was sufficient for the statistical analysis, selection bias could not be eliminated because only 2,341 individuals (70.854%) among the approximately 3,304 faculty and HCWs at the medical institution agreed to participate in the study. Second, the accuracy of the serum antibody to SARS-CoV-2 tests, including iFlash-SARS-CoV-2, is still not very reliable because they are new diagnostic tests. Although the diagnostic accuracy of the iFlash-SARS-CoV-2 is high (27, 28), the study plan was to use the serum obtained from Japanese residents before the COVID-19 outbreak and to measure the specificity of iFlash-SARS-CoV-2 to confirm its high diagnostic accuracy.

In conclusion, a serum IgG antibody against SARS-CoV-2 test was conducted among 2,320 faculty and HCWs at a medical institution in Tokyo, Japan, revealing an IgG antibody prevalence rate of 0.862%, for which most participants were undiagnosed due to their infection having been mild or asymptomatic. The participants with a history of a fever and dysgeusia or dysosmia tended to have positive results. The IgG antibody prevalence rate for faculty and HCWs providing medical care for COVID-19 patients using adequate protection was relatively low. To reduce the risk of COVID-19 spread in medical institutions, faculty or HCWs with a fever and hypogeusia or hyposmia should excuse themselves from work as soon as possible. It is also critical to take standard and necessary transmission-based precautions when working at medical institutions.

**The authors state that they have no Conflict of Interest (COI).**

**Acknowledgement**

The authors thank Kumiko Matsuzaki (Keio University, Tokyo, Japan) and Kei Yamato (Keio University, Tokyo, Japan) for their assistance in obtaining consent from the participants.

**Financial support**

This work was supported by Keio Gijuku Academic Development Funds [T.N.], the Daiwa Securities Health Foundation [T. N.], and Keio Donner Project Funds.

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