Global Health & Medicine. 2023; 5(1):5-14.

ORIGINAL ARTICLE

DOI: 10.35772/ghm.2022.01060

Specific COVID-19 risk behaviors and the preventive effect of personal protective equipment among healthcare workers in Japan

Reiko Shimbashi[1], Teiichiro Shiino[2,3], Akira Ainai[4], Saya Moriyama[5], Satoru Arai[1], Saeko Morino[1], Sayaka Takanashi[1], Takeshi Arashiro[1], Motoi Suzuki[1], Yukimasa Matsuzawa[1], Kenichiro Kato[6], Mitsuru Hasegawa[7], Rie Koshida[8], Masami Kitaoka[8], Takafumi Ueno[9], Hidefumi Shimizu[10], Hiroyoshi Yuki[11], Tomoko Takeda[12], Fukumi Nakamura-Uchiyama[13], Kashiya Takasugi[14], Shun Iida[4], Tomoe Shimada[15], Hirofumi Kato[16], Tsuguto Fujimoto[17], Naoko Iwata-Yoshikawa[4], Kaori Sano[4], Souichi Yamada[16], Yudai Kuroda[18], Kazu Okuma[19,20], Kiyoko Nojima[19], Noriyo Nagata[4], Shuetsu Fukushi[16], Ken Maeda[18], Yoshimasa Takahashi[5], Tadaki Suzuki[4], Makoto Ohnishi[21], Keiko Tanaka-Taya[1,22,*]

[1] Center for Surveillance, Immunization, and Epidemiologic Research, National Institute of Infectious Diseases, Shinjuku, Tokyo, Japan;
[2] Center for Clinical Sciences, National Center for Global Health and Medicine, Shinjuku, Tokyo, Japan;
[3] AIDS Research Center, National Institute of Infectious Diseases, Shinjuku, Tokyo, Japan;
[4] Department of Pathology, National Institute of Infectious Diseases, Shinjuku, Tokyo, Japan;
[5] Research Center for Drug and Vaccine Development, National Institute of Infectious Diseases, Shinjuku, Tokyo, Japan;
[6] Nakanoegota Hospital, Nakano, Tokyo, Japan;
[7] Okabe Hospital, Kanazawa, Ishikawa, Japan;
[8] Kanazawa City Health Center, Kanazawa, Ishikawa, Japan;
[9] Fukuoka Kinen Hospital, Fukuoka, Fukuoka, Japan;
[10] JCHO Tokyo Shinjuku Medical Center, Shinjuku, Tokyo, Japan;
[11] Yamada Memorial Hospital, Sumida, Tokyo, Japan;
[12] Chuo Public Health Center, Chuo, Tokyo, Japan;
[13] Tokyo Metropolitan Bokutoh Hospital, Sumida, Tokyo, Japan;
[14] Yoron Tokushukai Hospital, Oshima, Kagoshima, Japan;
[15] Center for Field Epidemic Intelligence, Research and Professional Development, National Institute of Infectious Diseases, Shinjuku, Tokyo, Japan;
[16] Department of Virology 1, National Institute of Infectious Diseases, Shinjuku, Tokyo, Japan;
[17] Center for Emergency Preparedness and Response, National Institute of Infectious Diseases, Shinjuku, Tokyo, Japan;
[18] Department of Veterinary Science, National Institute of Infectious Diseases, Shinjuku, Tokyo, Japan;
[19] Department of Safety Research on Blood and Biological Products, National Institute of Infectious Diseases, Musashimurayama, Tokyo, Japan;
[20] Department of Microbiology, Kansai Medical University, Hirakata, Osaka, Japan;
[21] Deputy Director-General, National Institute of Infectious Diseases, Shinjuku, Tokyo, Japan;
[22] Kanagawa Prefectural Institute of Public Health, Chigasaki, Kanagawa, Japan.

Abstract: As coronavirus disease 2019 (COVID-19) outbreaks in healthcare facilities are a serious public health concern, we performed a case-control study to investigate the risk of COVID-19 infection in healthcare workers. We collected data on participants' sociodemographic characteristics, contact behaviors, installation status of personal protective equipment, and polymerase chain reaction testing results. We also collected whole blood and assessed seropositivity using the electrochemiluminescence immunoassay and microneutralization assay. In total, 161 (8.5%) of 1,899 participants were seropositive between August 3 and November 13, 2020. Physical contact (adjusted odds ratio 2.4, 95% confidence interval 1.1-5.6) and aerosol-generating procedures (1.9, 1.1-3.2) were associated with seropositivity. Using goggles (0.2, 0.1-0.5) and N95 masks (0.3, 0.1-0.8) had a preventive effect. Seroprevalence was higher in the outbreak ward (18.6%) than in the COVID-19 dedicated ward (1.4%). Results showed certain specific risk behaviors of COVID-19; proper infection prevention practices reduced these risks.

***Keywords*:** risk factors, seroepidemiology, personal protective equipment

Introduction

Since the World Health Organization declared the coronavirus disease 2019 (COVID-19) pandemic in March 2020, data on disease control measures have accumulated (*1-3*) and vaccines have been made available. However, owing to the emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants and breakthrough infections, COVID-19 is still spreading worldwide in 2022 (*4*). In particular, SARS-CoV-2 infection in nosocomial settings remains a public health concern (*5*). Although guidance on infection prevention strategies for healthcare practices is provided by the state or agency (*6,7*), COVID-19 outbreaks in healthcare facilities continue to occur (*8*). Even after more than two years after the beginning of the pandemic, the spread of the SARS-CoV-2 infection in healthcare facilities is an important issue as it can lead to a shortage of healthcare workers and restrictions on medical care in hospitals. The risk of SARS-CoV-2 infection in healthcare workers needs to be clarified to protect healthcare workers and preserve medical resources.

In Japan, approximately 22 million COVID-19 cases were reported by October 2022 (9). Analyzing the data of the early pandemic period, *i.e.*, the period before the spread of COVID-19 in the community, would be useful for assessing the risk of SARS-CoV-2 infection limited to healthcare facilities.

Front-line healthcare workers are highly exposed to infection through contact with patients with COVID-19; and, they are at an increased risk of infection compared with the general public (*2,3,10*). Previous studies have reported a high seroprevalence of COVID-19 among healthcare workers having direct contact with patients with COVID-19 (*3,11*). Two cohort studies demonstrated that the improper use or lack of personal protective equipment (PPE) was associated with a higher prevalence of COVID-19 (*10,12*). Although face masks reduce the risk of infection (*11,13,14*), evidence on the efficacy of other PPEs and quantitative assessments are limited. Overall, specific risk behaviors for SARS-CoV-2 infection during hospital work are not fully understood.

We conducted this study to investigate COVID-19 risk among healthcare workers in Japan. Additionally, we also explored the differences in seropositivity across diverse occupations not limited to front-line healthcare workers.

Materials and Methods

Study design and participants

We performed a case-control study to evaluate the association between SARS-CoV-2 infection and possible risk factors in nosocomial outbreak settings. We assessed sociodemographic factors, contact history with patients with COVID-19, and PPE use as possible risk factors among staff in seven facilities (Supplementary Table S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=63*). SARS-CoV-2 infection was defined by a positive result of a serologic test performed using the methods described here. Only participants with both epidemiological information and antibody results available were included. As we focused on the risk in nosocomial settings, participants with contact histories outside their facilities were excluded from the analyses.

Participants were recruited from hospitals where COVID-19 outbreaks occurred between March and August 2020 in Japan (*15*). Not only front-line healthcare workers but also affiliated workers such as cleaning staff were included.

We appointed a representative for each participating hospital, who explained the study outline, benefits, and risks to all staff members. Participation in the study was voluntary and all the participants provided written informed consent. This study was approved by the ethics committee of the National Institute of Infectious Diseases (NIID) (No. 1177) and conducted according to the principles in the Declaration of Helsinki.

Procedures

An identification code was created for each participant, and only anonymized information was shared with the analysis team. The link between the participant's identification code and personal data was managed by the respective hospital representatives.

Blood sampling and questionnaire survey were conducted from August to November 2020 (Supplementary Figure S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=63*). The participants were required to provide their epidemiological information on a web-based questionnaire system using their smartphone or computer; the questionnaire comprised the following information: sociodemographic characteristics, underlying medical conditions, occupation, career, details and frequency of contact history with patients with COVID-19, PPE use, and polymerase chain reaction (PCR) results. Information on behavior of each participant during the outbreak period was obtained for data on contact history and PPE use. Data of PCR tests performed at each hospital prior to the serologic test in this study was obtained. The response status was regularly checked, and non-responders were alerted to answer the questions. Each participant was informed of the serologic test result through their personal page in the system. The page was set to be displayed only to the participants who answered the questionnaire so as to improve the completion rate.

The participants were divided into six age groups, each comprising 10 years, ranging from 20s to 70s and over. Their underlying disorders were grouped as immunodeficiency/malignancy and others. Career, defined as the number of years in their occupation, was classified into five groups, in multiples of five. Data on the type of ward was sought for participants whose facilities provided medical treatment for patients with COVID-19, and type of ward was classified as dedicated

COVID-19 ward (ward for the treatment of patients with COVID-19), outbreak ward (non-COVID-19 ward where an outbreak was detected among staff or in-patients), and non-outbreak ward (non-COVID-19 ward where no outbreak was detected among staff or in-patients). Participants who had contact history with patients with COVID-19 were required to provide the details and frequency of their contact (with or without the following actions: entering the room, contact with the surrounding environment, approach within 1 m, conversation, and physical contact). PPE use during treatment of patients with COVID-19 was evaluated as follows: used always, used sometimes, and not used. PPE included surgical masks, gloves, goggles, gowns or aprons, and N95 masks. As the situations where the use of N95 masks was recommended varied by facility, N95 mask use during aerosol-generating procedures was assessed as all participating facilities recommended its use.

Blood samples were collected at each hospital and transported to the NIID in cold chain. We tested for the anti-SARS-CoV-2 antibody using electrochemiluminescence immunoassay (ECLIA, Elecsys® Anti-SARS-CoV-2; Roche Diagnostics K.K., Basel, Switzerland) and microneutralization assay (NIID, Tokyo, Japan). Seropositivity was defined as a positive result for any of these tests, with a cut-off titer of 1.0 for the ECLIA and 1:5 for the microneutralization assay.

The ECLIA was performed on all the samples according to the manufacturer's instructions (*16*). The assay detects antibodies to SARS-CoV-2 nucleocapsid protein, including immunoglobulin G (IgG), using serum or plasma. The test for antibodies to nucleocapsid protein returns positive results in case of the SARS-CoV-2 infection, not the vaccination. The manufacturer has claimed a sensitivity of 99.5% (95% confidence interval [CI]: 88.1-100) based on the test results in symptomatic patients within 14 days post PCR diagnoses. The specificity was evaluated as 99.8% (95% CI: 99.7-99.9) from test results of samples collected before the emergence of SARS-CoV-2 (*16*). The cut-off index of the assay was defined as 1.0 by the manufacturer. The assay was performed as a screening test, and the screening-positivity criterion was set as 0.1 or higher in this study (*17*). Screening-positive cases were evaluated for SARS-CoV-2 microneutralizing antibody using the following method.

The microneutralization assay was developed at the NIID (*18*). Vero E6/TMPRSS2 cells and SARS-CoV-2 JPN/TY/WK-521 strain were used for the assay (*18*). The test serum was diluted in serial two-fold steps from 1:5 to 1:160 and the challenge virus (100 Tissue Culture Infectious Dose 50/50µl) was allowed to react at 37°C for 1 hour. Next, VeroE6/TMPRSS cells were added to the mixture and incubated at 37°C for 5 days. After the incubation, the cytopathic effect (CPE) of each well was observed under an inverted microscope. The microneutralization titer was evaluated after formalin fixation and crystal violet staining. The highest dilution of wells without CPE was defined as the microneutralization titer.

Statistical analyses

The characteristics of participants with seropositivity were compared using Pearson chi-squared test or Fisher exact test, as appropriate. The outcome of interest was a positive serologic test for SARS-CoV-2, and the possible risk factors were sociodemographic factors, contact history with patients with COVID-19, and PPE use. The risk factors were evaluated using adjusted odds ratios (OR) with 95% CIs using multivariable logistic regression models. Of the significant factors explored using univariable analyses, those affecting the adjusted ORs were included in the final models as possible confounding factors (Supplementary Table S2, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=63*). The missing values were coded as "no record" and included in the analyses. All analyses were performed using STATA version 15 (StataCorp, College Station, Texas).

Results

A total of 2,059 employees were enrolled in this study (Figure 1). Of these, 124 did not answer the questionnaire, two did not undergo the serologic test, and 34 had contact history with COVID-19-infected persons outside their facility. After excluding these cases, 1,899 participants were included in the analyses.

Participating facilities were distributed in four out of eight regions in Japan (Supplementary Table

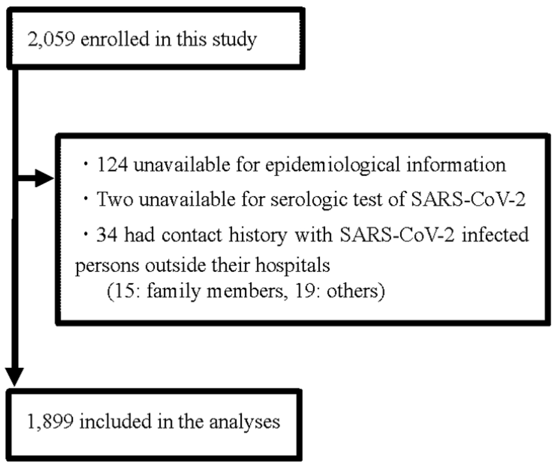

Figure 1. Study flow diagram. We recruited the study participants voluntarily among healthcare workers working at seven hospitals where outbreaks of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) occurred between March and August 2020 in Japan. A total of 1,899 participants were included in the analyses, excluding those who were unavailable for epidemiological information or the result of serologic test and those who had contact with SARS-CoV-2 infected persons outside their hospitals.

S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=63*). Three of these facilities had provided medical treatment to COVID-19 patients during each outbreak period. The outbreaks were detected from March to August 2020 and lasted weeks to months (Supplementary Figure S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=63*).

Blood collection was conducted from August 3 to November 13, 2020, and the period from outbreak to blood sampling was about 2 weeks to 4 months (Supplementary Figure S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=63*). The microneutralization assay was performed on 205 samples that screened positive (Table 1). Of these, 140 samples had a microneutralization titer of 1:5 or more, and 21 had an antibody titer of 1 or more on the ECLIA and a microneutralization titer of less than 1:5. A total of 161 samples (8.5%, 95% CI 7.3-9.8) were seropositive. We classified 161 seropositive participants as cases and 1738 seronegative participants as controls. Seropositivity proportion varied by facility, ranging from 24.4% (33 of 135, 95% CI 17.5-32.6) to 1.0% (2 of 196, 95% CI 0.1-3.6; Supplementary

Table 1. Results of the serologic test for severe acute respiratory syndrome coronavirus 2 among healthcare workers in Japan between August and November, 2020

		Total, *n*	Microneutralization titer, *n*					
			< 1:5	1:5	1:10	1:20	1:40	1:80
Antibody titer (ECLIA)	< 0.1	1,694	NA[a]	NA	NA	NA	NA	NA
	≥ 0.1, < 1	46	44	0	2	0	0	0
	≥ 1	159	21	40	47	36	10	5

ECLIA: electrochemiluminescence immunoassay; NA: not applicable; [a]Cases that showed < 0.1 on the ECLIA and were not tested on the microneutralization assay.

Table 2. Sociodemographic characteristics of participants by seropositivity

Variables	All participants, *n* (%)	Seropositive[a], *n* (%)	Seronegative, *n* (%)	*p* value
Sex				0.003
Male	583 (31)	32 (20)	551 (32)	
Female	1,315 (69)	129 (80)	1,186 (68)	
Unknown	1 (0)	0 (0)	1 (0)	
Age group (years)				0.001
≤ 30	609 (32)	72 (45)	537 (31)	
31-40	473 (25)	41 (25)	432 (25)	
41-50	415 (22)	21 (13)	394 (23)	
51-60	270 (14)	14 (9)	256 (15)	
61-70	107 (6)	10 (6)	97 (6)	
≥ 71	25 (1)	3 (2)	22 (1)	
Underlying disorder				0.284
Immunodeficiency or malignancy	33 (2)	3 (2)	30 (2)	
Others	564 (30)	48 (30)	516 (30)	
No underlying disorders	1,260 (66)	103 (64)	1,157 (67)	
Unknown	42 (2)	7 (4)	35 (2)	
Occupation				NA[b]
Office worker	165 (9)	5 (3)	160 (9)	
Doctor	248 (13)	16 (10)	232 (13)	
Nurse	836 (44)	102 (63)	734 (42)	
Nursing assistant	103 (5)	16 (10)	87 (5)	
Rehabilitation staff	105 (6)	7 (4)	98 (6)	
Radiologist	99 (5)	2 (1)	97 (6)	
Pharmacist	39 (2)	1 (1)	38 (2)	
Nutritionist	34 (2)	0 (0)	34 (2)	
Laboratory technician	89 (5)	0 (0)	89 (5)	
Social worker	23 (1)	0 (0)	23 (1)	
Psychologist	3 (0)	0 (0)	3 (0)	
Caregiver	25 (1)	1 (1)	24 (1)	
Cleaning staff	17 (1)	4 (2)	13 (1)	
Others	113 (6)	7 (4)	106 (6)	
Career (years)				0.056
≤ 5	704 (37)	74 (46)	630 (36)	
6-10	412 (22)	38 (24)	374 (22)	
11-20	440 (23)	27 (17)	413 (24)	
21-30	218 (11)	13 (8)	205 (12)	
≥ 31	125 (7)	9 (6)	116 (7)	

NA: not applicable; [a]Seropositive: Microneutralization titer ≥ 5 or antibody titer by ECLIA ≥ 1; [b]The data were too sparse for analysis.

Table 3. Seropositive proportion for severe acute respiratory syndrome coronavirus 2 by sociodemographic factors among healthcare workers in Japan between August and November, 2020

Variables	Seropositive proportion (%, 95% CI)	OR	*p* value	Adjusted OR[a]	*p* value
Sex					
Male	5.5 (3.8-7.7)	1 (ref)		1 (ref)	
Female	9.8 (8.3-11.5)	1.9 (1.3-2.8)	0.002	1.3 (0.8-2.1)	0.352
Age group (years)					
≤ 30	11.8 (9.4-14.7)	2.5 (1.5-4.2)	0.000	2.2 (1.2-3.9)	0.011
31-40	8.7 (6.3-11.6)	1.8 (1.0-3.1)	0.037	1.6 (0.8-2.8)	0.156
41-50	5.1 (3.2-7.6)	1 (ref)		1 (ref)	
51-60	5.2 (2.9-8.5)	1.0 (0.5-2.1)	0.942	1.0 (0.5-2.2)	0.970
61-70	9.3 (4.6-16.5)	1.9 (0.9-4.2)	0.100	2.3 (0.9-6.0)	0.095
≥ 71	12.0 (2.5-31.2)	2.6 (0.7-9.2)	0.151	1.4 (0.3-6.5)	0.684
Occupation					
Office worker	3.0 (1.0-6.9)	1 (ref)		1 (ref)	
Doctor	6.5 (3.7-10.3)	2.2 (0.8-6.1)	0.130	5.1 (1.6-15.9)	0.005
Nurse	12.2 (10.1-14.6)	4.4 (1.8-11.1)	0.001	5.4 (2.0-14.6)	0.001
Nursing assistant	15.5 (9.1-24.0)	5.9 (2.1-16.6)	0.001	9.0 (2.9-28.1)	0.000
Rehabilitation staff	6.7 (2.7-13.3)	2.3 (0.7-7.4)	0.168	1.8 (0.5-6.6)	0.346
Radiologist	2.0 (0.2-7.1)	0.7 (0.1-3.5)	0.623	0.8 (0.1-4.3)	0.749
Pharmacist	2.6 (0.1-13.5)	0.8 (0.1-7.4)	0.877	0.7 (0.1-6.9)	0.780
Nutritionist	0 (0-10.3)	NA	NA	NA	NA
Laboratory technician	0 (0-4.1)	NA	NA	NA	NA
Social worker	0 (0-14.8)	NA	NA	NA	NA
Psychologist	0 (0-70.8)	NA	NA	NA	NA
Caregiver	4.0 (0.1-20.4)	1.3 (0.1-11.9)	0.797	1.9 (0.2-19.1)	0.568
Cleaning staff	23.5 (6.8-49.9)	9.8 (2.4-41.2)	0.002	22.7 (3.9-132.0)	0.001
Career (years)					
≤ 5	10.5 (8.3-13.0)	1 (ref)		1 (ref)	
6-10	9.2 (6.6-12.4)	0.9 (0.6-1.3)	0.490	0.7 (0.5-1.2)	0.242
11-20	6.1 (4.1-8.8)	0.6 (0.4-0.9)	0.012	0.8 (0.4-1.4)	0.376
21-30	6.0 (3.2-10.0)	0.5 (0.3-1.0)	0.048	0.9 (0.4-2.0)	0.781
≥ 31	7.2 (3.3-13.2)	0.7 (0.3-1.4)	0.259	1.2 (0.4-3.8)	0.696

CI: confidence interval; OR: odds ratio; NA: not applicable; [a]Adjusted by sex, age, hospital, occupation, and contact history with coronavirus disease 2019 patients.

Table S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=63*).

Women accounted for 69.3% (1,315 of 1,899) of the participants and most seropositive cases were also women (80.1%, 129 of 161; Table 2). The number of seropositive participants was the highest for the age group of 20s (44.7%, 72 of 161) and decreased with age. The largest number of participants were nurses (44.0%, 836 of 1,899), followed by doctors (13.1%, 248 of 1,899) and office workers (8.7%, 165 of 1,899). About two-thirds of seropositive participants were nurses (102 of 161, 63.4%), and 9.9% each were doctors (16 of 161) and nursing assistants (16 of 161). None of the nutritionists, laboratory technicians, or social workers had positive serologic tests. The characteristics of underlying disorders and career were similar between seropositive and seronegative participants.

Participants in their 20s had increased odds of seropositivity compared with those in their 40s (aOR 2.2, 95% CI 1.2-3.9: Table 3). The odds of seropositivity in doctors (aOR 5.1, 95% CI 1.6-15.9), nurses (aOR 5.4, 95% CI 2.0-14.6), nursing assistants (aOR 9.0, 95% CI 2.9-28.1), and cleaning staff (aOR 22.7, 95% CI 3.9-132.0) were higher than those among office workers. Seropositivity odds were not higher in women than in men. We could not find any association between career and seropositivity after controlling for confounders.

Having contact history with COVID-19 patients was associated with seropositivity (aOR 4.8, 95% CI 2.8-8.1; Table 4). The group with physical contact with COVID-19 patients had a higher seropositive proportion than the group without it (aOR 2.4, 95% CI 1.1-5.6). The seropositivity of the participants who performed aerosol-generating procedures for COVID-19 patients was higher than those who did not (aOR 1.9, 95% CI 1.1-3.2; Table 5). No association was found between other contact histories and seropositivity (Table 4). Total number of contact days and average contact time per day were analyzed for contact frequency with COVID-19 patients, but we did not find any association between these factors and COVID-19 infection.

Participants who used goggles all the time during medical procedures (aOR 0.2, 95% CI 0.1-0.5; Table 5), and those who used them occasionally (aOR 0.5, 95% CI 0.2-1.0), were less infected than those who did not. No association was found between infection and the use of surgical masks, gloves, and gowns, regardless of their frequency of use. The group who always used N95

Table 4. Seropositive proportion for severe acute respiratory syndrome coronavirus 2 by contact history with coronavirus disease 2019 patients among healthcare workers in Japan between August and November, 2020

Variables	Number of seropositive participants	Seropositive proportion (%, 95% CI)	OR	*p* value	Adjusted OR	*p* value
Any contact history with COVID-19 patients[a]						
Yes	125/1,011	12.4 (10.4-14.6)	5.3 (3.3-8.5)	0.000	4.8 (2.8-8.1)	0.000
No	20/768	2.6 (1.6-4.0)	1 (ref)		1 (ref)	
The following analyses are among the participants who had any contact history with COVID-19 patients.						
(Details of contact history[b])						
Entering the room						
Yes	105/733	14.3 (11.9-17.1)	2.9 (1.6-5.3)	0.000	0.8 (0.3-2.0)	0.647
No	13/239	5.4 (2.9-9.1)	1 (ref)		1 (ref)	
Contact with the surrounding environment						
Yes	101/660	15.3 (12.6-18.3)	3.5 (2.0-6.1)	0.000	1.0 (0.4-2.3)	0.937
No	15/304	4.9 (2.8-8.0)	1 (ref)		1 (ref)	
Approach within 1m						
Yes	115/875	13.1 (11.0-15.6)	3.4 (1.2-9.3)	0.020	1.8 (0.5-5.9)	0.356
No	4/93	4.3 (1.2-10.6)	1 (ref)		1 (ref)	
Conversation						
Yes	111/819	13.6 (11.3-16.1)	3.2 (1.5-7.1)	0.003	2.5 (1.0-6.4)	0.051
No	7/151	4.6 (1.9-9.3)	1 (ref)		1 (ref)	
Physical contact						
Yes	104/648	16.0 (13.3-19.1)	3.5 (2.1-6.0)	0.000	2.4 (1.1-5.6)	0.037
No	17/331	5.1 (3.0-8.1)	1 (ref)		1 (ref)	
(Frequency of contact history[a])						
Total days of contact						
≤ 3	28/356	7.9 (5.3-11.2)	1 (ref)		1 (ref)	
4-7	24/156	15.4 (10.1-22.0)	2.1 (1.2-3.8)	0.011	1.4 (0.7-2.7)	0.307
8-14	21/122	17.2 (11.0-25.1)	2.4 (1.3-4.5)	0.004	1.5 (0.8-3.0)	0.237
15-30	23/132	17.4 (11.4-25.0)	2.5 (1.4-4.5)	0.003	1.7 (0.9-3.3)	0.131
≥ 31	20/182	11.0 (6.8-16.5)	1.4 (0.8-2.6)	0.231	1.0 (0.5-2.1)	0.900
Average time of contact per day						
< 15min	23/327	7.0 (4.5-10.4)	1 (ref)		1 (ref)	
≥ 15min, < 1H	30/308	9.7 (6.7-13.6)	1.4 (0.8-2.5)	0.220	1.0 (0.5-1.9)	0.969
≥ 1H, < 2H	21/121	17.4 (11.1-25.3)	2.8 (1.5-5.2)	0.002	1.3 (0.6-2.6)	0.546
≥ 2H	48/206	23.3 (17.7-29.7)	4.0 (2.4-6.8)	0.000	1.5 (0.8-2.8)	0.251

CI: confidence interval; OR: odds ratio; COVID-19: coronavirus disease 2019; [a]Adjusted by sex, age, hospital, and occupation; [b]Adjusted by sex, age, hospital, occupation, entering the room, contact with the surrounding environment, approach within 1m, conversation, and physical contact.

masks during the aerosol-generating procedure had a lower seropositive proportion than the group who did not use them (aOR 0.3, 95% CI 0.1-0.8). No association was found between the group who used N95 masks occasionally and SARS-CoV-2 infection.

Only one of 71 workers in the COVID-19 ward was seropositive (seropositivity proportion 1.4%, 95% CI 0.04-7.6), while 35 of 188 were positive in the outbreak ward (18.6%, 95% CI 13.3-24.9; Figure 2). The seropositivity proportion in the non-outbreak ward (1.4%, 95% CI 0.6-2.9) was similar to that in the COVID-19 ward.

PCR results prior to the serologic test were obtained for 965 of 1,899 participants (Supplementary Table S3, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=63*). When both positive and negative PCR results were reported, the analyses were performed using positive results. Of the 121 participants who reported PCR positive results, 23 were seronegative. The duration from PCR to serologic test ranged from 96 to 192 days.

Discussion

This study revealed certain risk behaviors for SARS-CoV-2 infection in nosocomial settings: physical contact and aerosol-generating procedures with patients with COVID-19. Doctors, nurses, and nursing assistants whose work involved such risk behaviors were more infected than office workers. Among occupations not involving patient-care, cleaning staff had a high seroprevalence; therefore, infection prevention measures for this employee group are also important. Of the PPE, goggles and N95 masks prevented SARS-CoV-2 infection with dose-response relationships.

The total seroprevalence in participants in this study (8.5%, 95% CI 7.3-9.8; 161 of 1,899) was much higher than that in the general population in Japan (0.7%, 103 of 15,043), according to a survey conducted several months after our study (*20*). As such, the study was conducted at a time when the infection was not widespread in the community and was appropriate for assessing the risk of infection in health care institutions.

Table 5. Preventive effect of severe acute respiratory syndrome coronavirus 2 infection by using personal protective equipment among healthcare workers in Japan between August and November, 2020

Variables	Number of seropositive participants	Seropositive proportion (%, 95% CI)	OR	*p* value	Adjusted OR	*p* value
Any medical procedures for COVID-19 patients[a]						
Yes	94/607	15.5 (12.7-18.6)	2.1 (1.3-3.3)	0.001	1.5 (0.8-2.5)	0.170
No	27/337	8.0 (5.3-11.4)	1 (ref)		1 (ref)	
The following analyses[b] are among participants who performed any medical procedures for COVID-19 patients.						
Surgical masks use						
Always	86/539	16.0 (13.0-19.3)	1.6 (0.6-4.1)	0.365	1.0 (0.3-3.1)	0.993
Sometimes	3/21	14.3 (3.0-36.3)	1.4 (0.3-6.3)	0.690	0.9 (0.1-5.7)	0.918
Never	5/46	10.9 (3.6-23.6)	1 (ref)		1 (ref)	
Gloves use						
Always	62/466	13.3 (10.4-16.7)	0.5 (0.2-1.1)	0.069	0.5 (0.1-1.8)	0.302
Sometimes	23/103	22.3 (14.7-31.6)	0.9 (0.4-2.2)	0.804	0.6 (0.2-2.0)	0.384
Never	9/37	24.3 (11.8-41.2)	1 (ref)		1 (ref)	
Goggles use						
Always	39/363	10.7 (7.8-14.4)	0.4 (0.2-0.7)	0.001	0.2 (0.1-0.5)	0.000
Sometimes	28/124	22.6 (15.6-31.0)	1.0 (0.5-1.8)	0.956	0.5 (0.2-1.0)	0.041
Never	27/118	22.9 (15.7-31.5)	1 (ref)		1 (ref)	
Gowns or aprons use						
Always	53/396	13.4 (10.2-17.1)	0.7 (0.4-1.4)	0.320	1.5 (0.5-4.9)	0.483
Sometimes	28/135	20.7 (14.2-28.6)	1.2 (0.6-2.5)	0.612	1.4 (0.5-4.0)	0.537
Never	13/73	17.8 (9.8-28.5)	1 (ref)		1 (ref)	
Aerosol-generating procedures for COVID-19 patients[a]						
Yes	43/221	19.5 (14.5-25.3)	2.7 (1.7-4.1)	0.000	1.9 (1.1-3.2)	0.021
No	57/689	8.3 (6.3-10.6)	1 (ref)		1 (ref)	
The following analysis is among participants who performed aerosol-generating procedures for COVID-19 patients.						
N95 masks use[a]						
Always	22/153	14.4 (9.2-21.0)	0.3 (0.2-0.8)	0.008	0.3 (0.1-0.8)	0.022
Sometimes	6/23	26.1 (10.2-48.4)	0.7 (0.2-2.3)	0.586	0.5 (0.1-2.1)	0.321
Never	14/43	32.6 (19.1-48.5)	1 (ref)		1 (ref)	

CI: confidence interval; OR: odds ratio; COVID-19: coronavirus disease 2019; [a]Adjusted by sex, age, hospital, and occupation; [b]Adjusted by sex, age, hospital, occupation, and eye shield use.

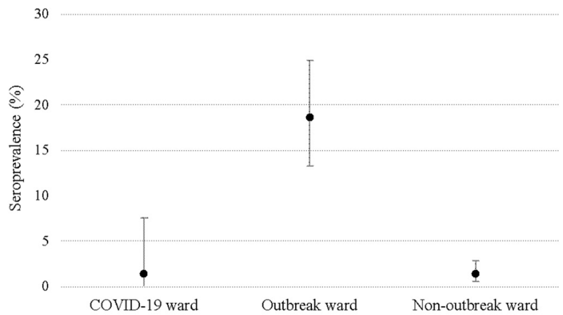

Figure 2. COVID-19 seroprevalence by ward type among healthcare workers in Japan between August and November, 2020. The wards were classified as COVID-19 ward (ward for the treatment of COVID-19 patients), outbreak ward (non-COVID-19 ward where outbreak was detected among staff or in-patients), and non-outbreak ward (non-COVID-19 ward where outbreak was not detected among staff or in-patients). The point estimates (dots) and 95% confidence intervals (lines) of COVID-19 seroprevalence are shown. The COVID-19 ward had the lower seroprevalence than the outbreak ward and similar to the non-outbreak ward.

So far, healthcare workers with patient contact had been reported to have high seropositivity (*3,11,13,21,22*). Our study also showed that doctors, nurses, and nursing assistants, *i.e.*, those who are engaged in patient care, were more infected than office workers. Rehabilitation staff, radiologists, and caregivers also had contact with patients, but they were not more infected than office workers. These results might reflect that they had a lesser chance of being included in risk behaviors such as aerosol-generating procedures. There were no seropositive participants among nutritionists, laboratory technicians, social workers, and psychologists. Similar to our study, fewer instances of infection in laboratory technicians were reported in previous studies (*2,23*), and the risk of infection from specimens obtained from patients with COVID-19 was low.

Cleaning staff showed a high seropositivity in our study. One case series also reported SARS-CoV-2 infection in cleaning staff who had no contact with patients with COVID-19 (*24*). Of the eight infected cleaners in the study, only one wore a face shield and had limited opportunities for infection prevention and control (IPC) training (*24*). In another observational study, cleaning staff had the highest seropositivity among staff working in hospitals with COVID-19 outbreaks (*23*). Of the 17 cleaning staff members who participated in our study, none reported a history of contact with patients with COVID-19. Two of the four cleaners who were seropositive had not undergone PCR testing during the outbreak period as they were not suspected to have SARS-CoV-2 infection by epidemiological investigation. Transmission by inhalation of infected aerosols in areas with patients with COVID-19 or through contact with contaminated fomites was suspected (*25*). Cleaning staff might be less trained in infection control than frontline healthcare workers and it is important to strengthen IPC training for them.

Healthcare workers in their 20s were more infected than those in their 40s. The susceptibility to SARS-CoV-2 infection by age group during the pre-vaccination period has been previously discussed. One systematic review and meta-analysis about household transmission of SARS-CoV-2 reported the secondary infection rate in family members with patients with COVID-19 to be low in children and high in older adults (*26*). In addition, population-based seroepidemiological surveys showed that children were less infected than adults, and the point estimates of seropositivity rates in people in their 40s and 50s were higher than those in other generations (*22,27*). We could not find reports of young adults being more susceptible to infection in the general population. Healthcare workers, meanwhile, have been reported to be more infected in the younger age group, similar to our study (*2,3*). Healthcare workers in their 20s might have more close contact with patients with COVID-19 than those in their 40s and 50s, and they might be unfamiliar with PPE use.

Physical contact with patients with COVID-19, the closest form of contact in our questionnaire, was considered a risk behavior for SARS-CoV-2 infection. The association between other contact behaviors with patients with COVID-19 (entering the room, contact with the surrounding environment, approach within 1 m, conversation) and seropositivity was unclear, but the point estimates of OR tended to be higher for closer contact.

The group that always used N95 masks during aerosol-generating procedures was found to be less infected, which was consistent with previous studies (*1,3,13*). However, there was no conclusive result on the association between surgical masks use and SARS-CoV-2 infection in our study. As N95 masks users were trained rigorously on the use of PPE, they might have been able to ensure appropriate fitting of their masks. However, surgical masks were worn by diverse hospital staff, and some participants might have been unfamiliar with wearing them correctly. In addition, some participants reported a lack of PPE during the study period. The preventive effect of surgical masks may have been underestimated owing to their improper wear or reuse. Among other PPE, the use of goggles prevented SARS-CoV-2 infection with dose-response relationships.

The outbreak ward had the highest seroprevalence in this study, and the COVID-19 ward had as few infections as the non-outbreak ward. By facility, seropositivity proportions were the highest in facilities that did not treat patients with COVID-19 during the study period. A questionnaire survey conducted in Japan from July to September 2021 also reported nosocomial outbreaks in facilities that did not provide COVID-19 inpatient care (*8*). The high seroprevalence in facilities that did not treat patients with COVID-19 suggests that viral transmission seemed to occur from an undiagnosed SARS-CoV-2-infected person with incomplete PPE use. In addition, the low seroprevalence in the COVID-19 ward indicated that risk factors could be modified with appropriate infection prevention.

In the 23 participants who previously tested positive by PCR and negative for serologic testing, the shortest duration from PCR to serologic test was 96 days. IgG for SARS-CoV-2 were produced approximately 2 weeks after infection (*28,29*). Therefore, the negative serologic results were not due to early testing. Longitudinal antibody responses against SARS-CoV-2 are under discussion. Some studies reported that neutralizing antibodies against SARS-CoV-2 had declined within a few months after disease onset (*30*), whereas others reported them to last for months to half a year (*31-33*). All 17 participants who reported the PCR test date had an interval of more than 3 months from the PCR to the antibody test, and 13 had more than half a year (median 184 days, range 96-192 days). This group might include those who had seroconverted, but the value decreased by the time the serologic test was conducted.

Multiple variants of SARS-CoV-2 have been reported during this pandemic. This study assessed the risk of wild-type virus infection, and the strength of the association between each risk factor and infection may not be consistent in the current epidemic of SARS-CoV-2 variants. However, quantitative risk assessments including a control group were limited in Japan, and the results of this study would be useful as fundamental data for future pandemics caused by strains with different infectivity.

This study has several strengths. First, we evaluated the SARS-CoV-2 infection through seroprevalence using a robust method. ECLIA was performed for screening in all cases, and the positivity criteria were set lower than the manufacturer's criteria so that false negatives were excluded. The screening-positive cases were tested using a microneutralization assay with high sensitivity and specificity. Second, we collected epidemiological information through a web-based system. As we were able to check the real-time response status, a high response rate (1,935 out of 2,059, 94.0%) could be obtained by sending appropriate reminders. Third, we recruited study participants regardless of prior PCR results. People with positive PCR results would be more concerned about the contexts in which they became infected than those who had negative PCR results or had not performed PCR. Therefore, we were able to minimize recall bias. Finally, as there were only a few community-acquired SARS-CoV-2 infections during our study period, we were able to assess the risk of infection limited to each healthcare facility.

Our study has several limitations. As this was a case-control study, causality could not be discussed. We could only show the strength of associations between SARS-CoV-2 infection and possible risk factors. However, the risk behaviors associated with SARS-CoV-2 infection in our study were consistent with other research methods such as cohort studies, systematic reviews, and meta-analyses (*2,3,11-13,34,35*). In addition, a dose-response relationship was found in the preventive effect of the use of goggles, which suggested a causal relationship. Second, wearing of PPE by patients with COVID-19 in contact with the participants seems to be a possible confounding factor, but we could not adjust this factor as we did not seek this information. Third, we could not exclude selection bias because we employed voluntary participation. Those with prior positive PCR results might have been more likely to not participate in the study than those who had negative results or were untested. Therefore, the seropositivity rate might be underestimated. However, it is unclear whether this bias raises or lowers the odds of risk behaviors. As information was collected through a self-reported questionnaire, recall bias could have occurred. Social desirability bias might influence the responses, especially with regard to PPE use. We tried to mitigate these information biases by communicating the serologic test result after questionnaire completion.

In conclusion, we investigated specific risk behaviors in nosocomial settings and the preventive effect of each PPE with a quantitative assessment. The differences in seropositivity rates by ward type suggested that these risk factors can be modified through appropriate infection prevention measures. COVID-19 outbreaks in hospitals which affect medical resources still remained a public health concern in 2022. Nonpharmaceutical intervention with proper PPE use remains critically important, especially for populations with inadequate IPC training.

Acknowledgements

We sincerely thank the following team members for their technical assistance: Ayaka Asano, Rie Kitamoto, Etsuko Kitagami, Moe Kumada, Sakiho Murakami, Yuta Tanaka, Kimiko Matsumoto, Hajime Kamiya, Toru Nanba, Kumiko Sukegawa, Mieko Kusaba, Noriaki Nagase, Masataka Tokita, Rieko Iwaki, Akiko Sataka, Harutaka Katano, Kenta Takahashi, Kenzo Tokunaga, Michiko Tanaka, Minoru Tobiume, Noriko Nakajima, Nozomi Shiwa-Sudo, Sho Miyamoto, Takayuki Kanno, Yuko Sato, Tsukasa Yamamoto, and Hitomi Kinoshita.

Funding: This work was supported by the Ministry of Health, Labor and Welfare (grant numbers 02-0091, JPMH20HA2007).

Conflict of Interest: The authors have no conflicts of interest to disclose.

References

1. Chu DK, Akl EA, Duda S, Solo K, Yaacoub S, Schünemann HJ; COVID-19 Systematic Urgent Review Group Effort (SURGE) study authors. Physical distancing, face masks, and eye protection to prevent person-to-person transmission of SARS-CoV-2 and COVID-19: A systematic review and meta-analysis. Lancet. 2020; 395:1973-1987.
2. Iversen K, Bundgaard H, Hasselbalch RB, *et al.* Risk of COVID-19 in health-care workers in Denmark: An observational cohort study. Lancet Infect Dis. 2020; 20:1401-1408.
3. Sims MD, Maine GN, Childers KL, Podolsky RH, Voss DR, Berkiw-Scenna N, Oh J, Heinrich KE, Keil H, Kennedy RH, Homayouni R. Coronavirus disease 2019 (COVID-19) seropositivity and asymptomatic rates in healthcare workers are associated with job function and masking. Clin Infect Dis. 2021; 73:S154-S162.
4. World Health Organization. COVID-19 Weekly Epidemiological Update. *https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---6-july-2022* (accessed July 11, 2022).
5. Tokyo Metropolitan Infectious Disease Surveillance Center. Number of cases by location of COVID-19 cluster. *http://idsc.tokyo-eiken.go.jp/diseases/2019-ncov/* (accessed December 28, 2022).
6. National Institute of Infectious Diseases. Infection control measures for COVID-19. *https://www.niid.go.jp/niid/images/epi/corona/2019nCoV-01-200602tbl.pdf* (accessed October 2, 2022).
7. World Health Organization. Infection prevention and control during health care when coronavirus disease (COVID-19) is suspected or confirmed. *https://www.who.int/publications/i/item/WHO-2019-nCoV-IPC-2021.1* (accessed December 31, 2022).
8. The Japanese Association for Infectious Diseases. The 3rd COVID-19 Nosocomial Infection Questionnaire Survey. *https://www.kansensho.or.jp/modules/news/index.php?content_id=318* (accessed December 28, 2022). (in Japanese)
9. Ministry of Health, Labor and Welfare. COVID-19 information. *https://covid19.mhlw.go.jp/en/* (accessed November 2, 2022).
10. Nguyen LH, Drew DA, Graham MS, *et al.* Risk of COVID-19 among front-line health-care workers and the general community: A prospective cohort study. Lancet Public Health. 2020; 5:e475-e483.
11. Chen Y, Tong X, Wang J, Huang W, Yin S, Huang R, Yang H, Chen Y, Huang A, Liu Y, Chen Y, Yuan L, Yan X, Shen H, Wu C. High SARS-CoV-2 antibody prevalence among healthcare workers exposed to COVID-19 patients. J Infect. 2020; 81:420-426.
12. Ran L, Chen X, Wang Y, Wu W, Zhang L, Tan X. Risk factors of healthcare workers with coronavirus disease 2019: A retrospective cohort study in a designated hospital of Wuhan in China. Clin Infect Dis. 2020; 71:2218-2221.
13. Martischang R, Iten A, Arm I, Abbas M, Meyer B, Yerly S,

Eckerle I, Pralong J, Sauser J, Suard JC, Kaiser L, Pittet D, Harbarth S. Severe acute respiratory coronavirus virus 2 (SARS-CoV-2) seroconversion and occupational exposure of employees at a Swiss university hospital: a large longitudinal cohort study. Infect Control Hosp Epidemiol. 2022; 43:326-333.
14. Kwon S, Joshi AD, Lo CH, *et al.* Association of social distancing and face mask use with risk of COVID-19. Nat Commun. 2021; 12:3737.
15. Kato H, Seki K, Maeda Y, Noda Y, Iinuma Y, Kitaoka M, Kiso K, Koshida R, Kurosu H, Yamagishi T, Shimada T, Suzuki M, Sunagawa T. Rapid response to a coronavirus disease 2019 (COVID-19) outbreak in a psychiatry hospital-Kanazawa City, Japan, March to April 2020. Antimicrob Steward Healthc Epidemiol. 2022; 2:e57.
16. Roche Diagnostics K.K. Elecsys® Anti-SARS-CoV-2 RUO. *https://diagnostics.roche.com/jp/ja/products/params/elecsys-anti-sars-cov-2.html* (accessed August 6, 2022). (in Japanese)
17. Public Health England. Evaluation of sensitivity and specificity of four commercially available SARS-CoV-2 antibody immunoassays. *https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/898437/Evaluation__of_sensitivity_and_specificity_of_4_commercially_available_SARS-CoV-2_antibody_immunoassays.pdf* (accessed March 28, 2022).
18. Ministry of Health, Labor and Welfare. Testing procedure of National Epidemiological Surveillance of Vaccine-Preventable Diseases. *https://www.niid.go.jp/niid/images/epi/yosoku/AnnReport/2021-99.pdf* (accessed August 10, 2022). (in Japanese)
19. Matsuyama S, Nao N, Shirato K, *et al.* Enhanced isolation of SARS-CoV-2 by TMPRSS2-expressing cells. Proc Natl Acad Sci U S A. 2020; 117:7001-7003.
20. Ministry of Health, Labor and Welfare. The seroprevalence of SARS-CoV-2 in general public. *https://www.mhlw.go.jp/content/000761671.pdf* (accessed January 26, 2022). (in Japanese)
21. Korth J, Wilde B, Dolff S, Anastasiou OE, Krawczyk A, Jahn M, Cordes S, Ross B, Esser S, Lindemann M, Kribben A, Dittmer U, Witzke O, Herrmann A. SARS-CoV-2-specific antibody detection in healthcare workers in Germany with direct contact to COVID-19 patients. J Clin Virol. 2020; 128:104437.
22. Chen X, Chen Z, Azman AS, Deng X, Sun R, Zhao Z, Zheng N, Chen X, Lu W, Zhuang T, Yang J, Viboud C, Ajelli M, Leung DT, Yu H. Serological evidence of human infection with SARS-CoV-2: A systematic review and meta-analysis. Lancet Glob Health. 2021; 9:e598-609.
23. Alkurt G, Murt A, Aydin Z, *et al.* Seroprevalence of coronavirus disease 2019 (COVID-19) among health care workers from three pandemic hospitals of Turkey. PLoS One. 2021; 16:e0247865.
24. Kurosu H, Watanabe K, Kurosawa K, *et al.* Possible contact transmission of SARS-CoV-2 in healthcare settings in Japan, 2020-2021. Infect Control Hosp Epidemiol. 2022; 43:1296-1298.
25. Centers for Disease Control and Prevention. Science Brief: SARS-CoV-2 and surface (fomite) transmission for indoor community environments. *https://www.cdc.gov/coronavirus/2019-ncov/more/science-and-research/surface-transmission.html* (accessed March 30, 2022).
26. Madewell ZJ, Yang Y, Longini IM, Halloran ME, Dean NE. Household transmission of SARS-CoV-2: A systematic review and meta-analysis. JAMA Netw Open. 2020; 3:e2031756.
27. Le Vu S, Jones G, Anna F, *et al.* Prevalence of SARS-CoV-2 antibodies in France: Results from nationwide serological surveillance. Nat Commun. 2021; 12:3025.
28. Borremans B, Gamble A, Prager KC, Helman SK, McClain AM, Cox C, Savage V, Lloyd-Smith JO. Quantifying antibody kinetics and RNA detection during early-phase SARS-CoV-2 infection by time since symptom onset. Elife. 2020; 9:e60122.
29. Altawalah H. Antibody responses to natural SARS-CoV-2 infection or after COVID-19 vaccination. Vaccines. 2021; 9:910.
30. Marot S, Malet I, Leducq V, *et al.* Rapid decline of neutralizing antibodies against SARS-CoV-2 among infected healthcare workers. Nat Commun. 2021; 12:844.
31. Yamayoshi S, Yasuhara A, Ito M, *et al.* Antibody titers against SARS-CoV-2 decline, but do not disappear for several months. EClinicalMedicine. 2021; 32:100734.
32. Goto A, Go H, Miyakawa K, *et al.* Sustained neutralizing antibodies 6 months following infection in 376 Japanese COVID-19 survivors. Front Microbiol. 2021; 12:661187.
33. Gudbjartsson DF, Norddahl GL, Melsted P, *et al.* Humoral immune response to SARS-CoV-2 in Iceland. N Engl J Med. 2020; 383:1724-1734.
34. Gómez-Ochoa SA, Franco OH, Rojas LZ, Raguindin PF, Roa-Díaz ZM, Wyssmann BM, Guevara SLR, Echeverría LE, Glisic M, Muka T. COVID-19 in health-care workers: A living systematic review and meta-analysis of prevalence, risk factors, clinical characteristics, and outcomes. Am J Epidemiol. 2021; 190:161-175.
35. Gholami M, Fawad I, Shadan S, Rowaiee R, Ghanem H, Khamis AH, Ho SB. COVID-19 and healthcare workers: A systematic review and meta-analysis. Int J Infect Dis. 2021; 104:335-346.

Received October 6, 2022; Revised January 19, 2023; Accepted January 27, 2023.

Released online in J-STAGE as advance publication February 5, 2023.

**Address correspondence to*:
Keiko Tanaka-Taya, Kanagawa Prefectural Institute of Public Health, 1-3-1 Shimomachiya, Chigasaki, Kanagawa 253-0087, Japan.
E-mail: ktaya@biglobe.jp