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Seroprevalence of SARS-CoV-2 antibodies among hospital staff in rural Central Fukushima, Japan: A historical cohort study

Yurie Kobashi [a,b,*], Yoshitaka Nishikawa [a], Takeshi Kawamura [c,d], Tatsuhiko Kodama [c], Yuzo Shimazu [e], Daiji Obara [a], Tianchen Zhao [b], Masaharu Tsubokura [a,b]

[a] Department of General Internal Medicine, Hirata Central Hospital, Hirata, Ishikawa District, Fukushima, Japan
[b] Department of Radiation Health Management, Fukushima Medical University School of Medicine, Fukushima City, Fukushima, Japan
[c] Laboratory for Systems Biology and Medicine, Research Center for Advanced Science and Technology, The University of Tokyo, Tokyo 153-8904, Japan
[d] Proteomics Laboratory, Isotope Science Center, The University of Tokyo, Tokyo 113-0032, Japan
[e] Southern Tohoku Research Institute for Neuroscience, 7-115, Yatsuyamada, Koriyama, Fukushima 963-8563, Japan

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ABSTRACT

Performing a cohort-based SARS-CoV-2 antibody assay is crucial for understanding infection status and future decision-making. The objective of this study was to examine consecutive antibody seroprevalence changes among hospital staff, a high-risk population. A two-time survey was performed in May and October 2020 for 545 hospital staff to investigate the changes in the results of the rapid kit test and chemiluminescence immunoassay (CLIA). The seroprevalence of each assay was summarized at both the survey periods. The proportion of seropositive individuals in the CLIA for each survey period and the number of confirmed COVID-19 cases in Central Fukushima were then compared. We chose 515 participants for the analysis. The proportion of IgM seroprevalence in CLIA increased from 0.19% in May to 0.39% in October, and IgG seroprevalence decreased from 0.97% in May to 0.39% in October. The proportion of IgM seroprevalence in the rapid kit test decreased from 7.96% in May to 3.50% in October, and IgG seroprevalence decreased from 7.77% in May to 2.14% in October.

The IgG and IgM antibody seroprevalence among hospital staff in rural Central Fukushima decreased; the seroprevalence among hospital staff was consistent with the number of confirmed COVID-19 cases in the Central Fukushima area. Although it is difficult to interpret the results of the antibody assay in a population with a low prior probability, constant follow-up surveys of antibody titers among hospital staff had several merits in obtaining a set of criteria regarding the accuracy of measures against COVID-19 and estimating the COVID-19 infection status among hospital staff.

1. Introduction

Laboratory testing in a cohort is vital to estimate the prevalence of diseases, to identify them at early stages, and to offer important insights about diseases. During the spread of COVID-19 worldwide, understanding its infection status in the cohort was essential for public health decision-making. To this end, various assays, including polymerase chain reaction (PCR) assay, chemiluminescence immunoassay (CLIA), immunochromatography (ICG) assay, and other assays have been performed. In particular, antibody assays are useful for evaluating the extent of a disease in the population because they are associated with past infection status [1]. Consequently, large-scale population-based antibody examinations have been performed, and these studies have provided information on antibody incidence in the cohort as well as allowed for comparisons of results with other assays and inferences regarding asymptomatic patients [2,3]. Thus, performing a cohort-based COVID-19 antibody test is crucial in terms of public health for understanding the infection status and future decision-making.

To date, numerous antibody tests have been conducted to understand the status of COVID-19 in the population. In particular, follow-up studies in the cohort have provided principal insights into the spread of SARS-CoV2-2019 in the population, including direct information on and estimates of infection proportions in various regions [4,5]. In addition, hospital staff are considered a priority population for estimated infection proportion; hospital staff are reported to have a higher proportion of antibody positivity than the general population [6]. Thus, antibody

* Corresponding author at: Department of General Internal Medicine, Hirata Central Hospital, Hirata, Ishikawa district, Fukushima 963-8202, Japan.
E-mail address: yurie-s@umin.ac.jp (Y. Kobashi).

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testing of hospital staff has been conducted to protect those on the frontline [7,8]. Nevertheless, except for a small number of sample size surveys, few follow-up studies on antibody testing among hospital staff have been conducted [9].

Fukushima Prefecture, approximately 239 km north of Tokyo, is an area with high disaster frequency where approximately 1,850 thousand residents live. A large proportion of these residents live in the rural areas, which originally had poor health care resources; the shortage of these resources was amplified after disasters—particularly the Great East Japan earthquake [10,11]. Recently, in October 2020, it was confirmed that there were 388 COVID-19 positive patients in Fukushima Prefecture. Nevertheless, previous surveys have suggested that the seropositive antibody prevalence among hospital staff was relatively higher than expected in Japan [12,13]. More specifically, the Central Fukushima area, where there were 27 confirmed COVID-19 cases by October 2020, is one of the prefectures that reported the aforementioned prevalence [13]. Thus, the Central Fukushima area is a stable area for conducting a follow-up study on antibody seroprevalence among hospital staff.

The objective of this study was to examine the consecutive antibody seropositive proportion changes among hospital staff, a high-risk population, to help understand the impact of SARS-CoV2-2019 on the cohort. Antibody testing was conducted in May, the end of the first wave, and in October, during the second wave, among the staff of a health care group in rural Central Fukushima.

2. Method

2.1. Setting and study design

This was an observational cohort study. The Seireikai group is a private community-based health care group with hospitals, clinics, long-term care facilities, and daycare facilities as well as home visiting services in the Central Fukushima area of Japan. It runs Hirata Central Hospital, which is located in Hirata Village—a mountainous area that is one of the most resource-poor areas in Fukushima Prefecture. Hirata Central Hospital with 142 beds for inpatients is the only hospital in the area that accepts emergency patients. Moreover, approximately 650 staff work in the Seireikai group, and have taken efforts to protect patients and residents after the COVID-19 pandemic by establishing a PCR center and a specialized clinic for patients who had symptoms compatible with COVID-19, conducting regular meetings for infection control, and organizing a survey of SARS-CoV2-2019 RNA in the sewage line. The present survey was conducted as one of the countermeasures in this context. Most of the hospital staff were full-time workers; however, some of the doctors were part-time workers. The eligible study participants were hospital staff working in Seireikai Group who had completed both tests in May and October and agreed to participate in the study both in May and October 2020.

An initial blood test sampling was conducted between May 8 and May 28, 2020, during the end of the first wave of the pandemic in Japan, to determine the prevalence of COVID-19 antibodies among staff and to understand the infection status. The number of patients per day in Fukushima Prefecture and Central Fukushima is shown in Fig. 1 and Supplementary Fig. 1.

Blood samples were collected mainly by the Seireikai group medical staff (9 mL). To ensure the accuracy of predictive prevalence, the rapid kit test and CLIA were performed on the same blood sample in the first survey. The rapid kit test and CLIA test have different characteristics. The rapid kit test is easy to use, provides results quickly, and is cheap, whereas the CLIA test can determine the quantitative value in detail. Comparing the rapid kit test with the CLIA test provided more detailed information about the results and the relevance of the tests. Blood test sampling was again conducted between October 5 and October 23, 2020 to determine the consecutive changes of antibody seropositive prevalence and provide insight into understanding the consecutive changes in the infection status. The second sampling was done at the end of the second wave of the pandemic in Japan (see Fig. 1 and Supplementary Fig. 1 for the number of patients per day). Blood samples were collected mainly by Seireikai group medical staff (9 mL) in the second sampling as well. Rapid kit tests and CLIA were also conducted on the same blood samples in the second survey. Thus, two surveys were performed to investigate the changes in the results of the rapid test kit and CLIA. In addition, participants were asked questions about COVID-19 symptoms (fever since January 2020, confirmed COVID-19 cases among household members) when their consent forms were obtained in May and October. The staff could undergo PCR testing when medically necessary, such as when they had had contact with outpatients for whom COVID-19

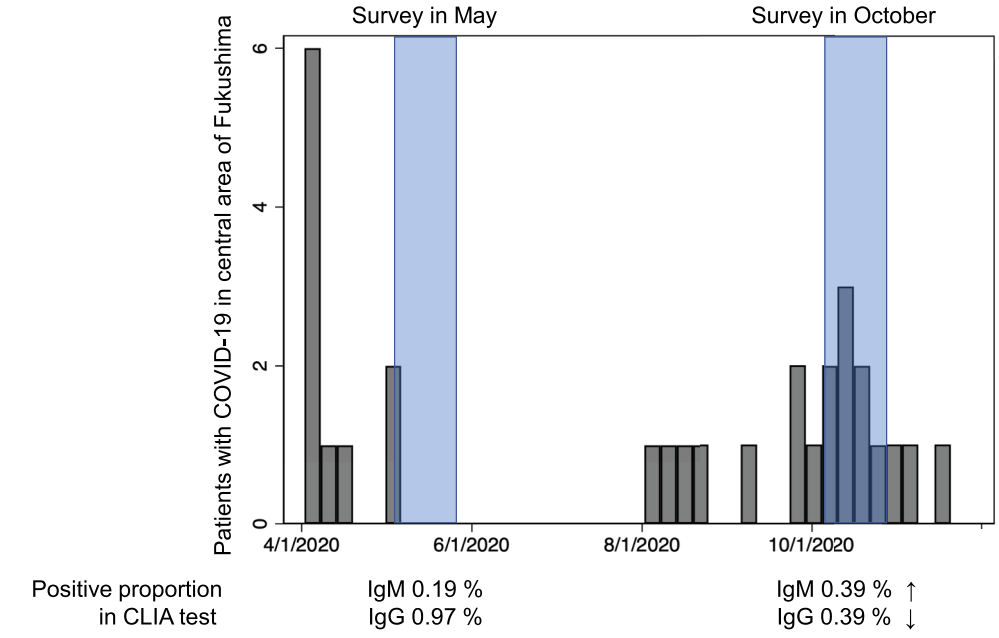

Fig. 1. Comparison between positive proportion in CLIA in each term and the number of confirmed cases of COVID-19 in the Central Fukushima area. CLIA = Chemiluminescence immunoassay. Population: 519,431 (1st April 2021).

infection could not be ruled out, or when validation tests were required to evaluate antibody test results. Moreover, staff could conduct PCR immediately if they had COVID-19 related symptoms and whenever required, except on weekends.

This study was approved by the ethics committee of Hirata Central Hospital (Ethics Committee ID: 2020–0427-1) and Fukushima Medical University (Ethics Committee ID: 2020–172), and all participants provided individual written informed consent for each blood test.

2.2. Laboratory analysis

The 2019-nCoV IgG/IgM kit (Vazyme Biotech Co., Ltd., YHLO Biotech, Shenzhen, China) was used for the rapid kit tests; the sensitivity and specificity of the rapid test kit were 91.54% and 97.02%, respectively [14]. The testing method process was followed by the official testing method, which was adequate [14]. The serum was used for the examination, and two independent laboratory technicians certified the line judgment. The examination procedure was performed at Hirata Central Hospital.

The CLIA quantitative antibody test was performed using a high-throughput assay apparatus, called iFlash 3000, and with assay reagents, iFlash-SARS-CoV-2 IgM/IgG (YHLO Biotech, Shenzhen, China). The examination procedure was performed at Tokyo University on May 16, 20, and 29, 2020, for the first survey and on November 10 and 11, 2020 for the second survey. Blood samples were brought from Hirata Central Hospital to Tokyo University. The testing method was performed according to official guidelines (Here, please refer to the official instruction manual for the iFlash immunoassay analyzer for SARS-CoV-2 IgG and IgM). The sensitivity and specificity of the CLIA test with - iFlash-SARS-CoV-2 IgG were 97.3% and 96.3%, respectively. The cutoff for the CLIA quantitative antibody test was 10 AU/mL. The S antigen—which may induce the production of neutralizing antibodies—and the N antigen were set as the targets for the antibody assay. The quality check test was conducted daily before the CLIA samples were measured. The expected value and the confidential range of the calibration reagent for each lot were demonstrated by the company, and the tests for participants were conducted after confirming that the values were within the demonstrated range. Reverse transcription polymerase chain reaction (RT-PCR) was performed using the LightCycler® 480 Instrument II [15].

2.3. Statistical analysis

First, we described the patient characteristics for each group as "tested IgM positive in the rapid kit test or CLIA" or "tested negative in all testing" in May and October, respectively. A multivariable adjusted logistic regression model was then used to estimate the odds ratio and 95% confidence intervals (CIs) for the association between IgM seropositive results and age, sex, occupation, and place of work. Participants who belonged to the group with all seronegative results were removed from the multivariable analysis because the group without seropositive result must be mandatorily removed from the multivariable analysis to conduct statistics analysis (e.g., doctors' group in Table 2(a)). The same analysis was also performed for IgG. Second, the proportion of seropositive results in the CLIA based on different testing periods and the number of confirmed COVID-19 cases in Central Fukushima Prefecture between March and November were compared to understand the proportion of seropositive results against the background of infection status in the area. Finally, the seroprevalence of each assay and term and complaints of fever were summarized in terms of IgM and IgG for all the hospital staff who were seropositive in at least one antibody test. Moreover, the numerical values of IgM and IgG from the CLIA in May were classified into ten groups (8 seronegative groups and two seropositive groups), and the median values for each group in May were determined; the results of the CLIA for each group for October were obtained as a follow-up, and the median value in October was then calculated as well (Supplementary Table 1). The proportion of seropositive individuals in the CLIA for different testing periods and the number of confirmed COVID-19 cases in Fukushima Prefecture between March and November were also compared (Supplementary Fig. 1). P-values less than 0.05 were considered statistically significant. All analyses were performed using STATA IC15 (Lightstone, Texas USA, version 15).

3. Results

The immunochromatography rapid kit test and the CLIA quantitative antibody test in May and October were conducted for 545 hospital staff; of these, we included 515 participants who worked as Seireikai group staff and agreed to participate in this study in the analysis. The median age (interquartile range) of the enrolled participants was 44 (34–56) years, with 383 (74.37%) women and 409 (79.42%) hospital staff. A total of 145 (28.16%) participants worked at the hospital, and 312 (60.58%) worked at long-term care facilities. Moreover, none of the 106 participants who performed PCR testing were found to be COVID positive (Table 1).

A total of 41 participants tested IgM positive for at least one rapid kit test or CLIA assay in May. Females had 5.88 times higher IgM positive prevalence than males. In addition, the proportion of IgM positive prevalence increased in the older groups (Table 2a). Moreover, a total of 20 participants tested IgM positive in at least one assay in October. The proportion of IgM positive prevalence was higher in those working at clinics than in those working at hospitals (Table 2b).

A total of 40 participants tested IgG positive in at least one assay of the rapid kit test or CLIA in May. The proportion of IgG prevalence was higher in those aged 45–64 years than in those aged 18–44 years. However, the difference in IgG prevalence between sexes was not significant (Table 3a). Subsequently, a total of 11 participants tested IgG positive in at least one assay in October. The proportion of IgG prevalence was not significantly associated with the participants' background characteristics (Table 3b).

The proportions of seropositive prevalence in CLIA in differen survey periods increased in IgM and decreased in IgG; however, the overall appearance of antibodies was low (Fig. 2). In the rapid kit test, the proportion of IgM seroprevalence decreased from 7.96% in May to 3.50% in October, and IgG seroprevalence in the rapid kit test decreased

Table 1
Participant's characteristics.

	n (%)
Gender	
Female	383 (74.37)
Male	132 (25.63)
Age, median [IQR]	44 [34–56]
Occupation	
Doctor	11 (2.14)
Nurse	103 (20.00)
Caregiver	237 (46.02)
Other medical staff	58 (11.26)
Office worker	50 (9.71)
Other non-medical staff	56 (10.87)
Working place	
Hospital	145 (28.16)
Clinic	48 (9.32)
Long term care health facility	312 (60.58)
Other	10 (1.94)
IgM positive in rapid kit test in May, [95% CI]	41 (7.96) [5.77–10.65]
IgG positive in rapid kit test in May, [95% CI]	40 (7.77) [5.61–10.43]
IgM positive in CLIA test in May, [95% CI]	1 (0.19) [0.00–1.08]
IgG positive in CLIA test in May, [95% CI]	5 (0.97) [0.32–2.25]
IgM positive in rapid kit test in Oct, [95% CI]	18 (3.50) [2.08–5.47]
IgG positive in rapid kit test in Oct, [95% CI]	11 (2.14) [1.07–3.79]
IgM positive in CLIA test in Oct, [95% CI]	2 (0.39) [0.05–1.40]
IgG positive in CLIA test in Oct, [95% CI]	2 (0.39) [0.05–1.40]

IQR; interquartile range, Oct; October, CI; confidential interval.

Table 2a
Comparison of participants' characteristics and IgM seropositive results in the rapid kit test or CLIA test in May and adjusted odds ratio for IgM seropositive results by gender, age, occupation, and workplace (n = 515).

	IgM (May)		Adjusted OR (95% CI) (n = 504)	*p* value
	Negative	Positive		
Gender				
Female	345 (90.08)	38 (9.92)	ref.	–
Male	129 (97.73)	3 (2.27)	0.17 (0.05–0.62)	**0.007**
Age				
18–44	247 (95.74)	11 (4.26)	ref.	–
45–64	194 (88.99)	24 (11.01)	3.12 (1.42–6.89)	**0.005**
65–78	33 (84.62)	6 (15.38)	5.54 (1.76–17.46)	**0.003**
Occupation				
Doctor	11 (100.00)	0 (0.00)	–	–
Nurse	96 (93.20)	7 (6.80)	0.66 (0.18–2.38)	0.53
Caregiver	215 (90.72)	22 (9.28)	1.66 (0.46–5.96)	0.43
Other medical staff	54 (93.10)	4 (6.90)	2.18 (0.48– 9.96)	0.32
Office worker	45 (90.00)	5 (10.00)	ref.	–
Other non-medical staff	53 (94.64)	3 (5.36)	0.53 (0.11–2.59)	0.43
Workplace				
Hospital	134 (21.41)	11 (7.59)	ref.	–
Clinic	43 (89.58)	5 (10.42)	2.36 (0.69–8.00)	0.166
Long-term care health facility	289 (92.63)	23 (7.37)	0.55 (0.22–1.38)	0.20
Other	8 (80.00)	2 (20.00)	2.93 (0.49–17.54)	0.24

Table 2b
Comparison of participants' characteristics and IgM seropositive results in the rapid kit test or CLIA test in October and adjusted odds ratio for IgM seropositive results by gender, age, occupation, and workplace (n = 515).

	IgM (October)		Adjusted OR (95% CI) (n = 438)	*p* value
	Negative	Positive		
Gender				
Female	365 (95.30)	18 (4.70)	ref.	–
Male	130 (98.48)	2 (1.52)	0.43 (0.09–2.08)	0.30
Age				
18–44	251 (97.29)	7 (2.71)	ref.	–
45–64	207 (94.95)	11 (5.05)	2.07 (0.75–5.69)	0.159
65–78	37 (94.87)	2 (5.13)	2.53 (0.46–13.98)	0.29
Occupation				
Doctor	11 (100.00)	0 (0.00)	–	–
Nurse	101 (98.06)	2 (1.94)	0.45 (0.06–3.17)	0.42
Caregiver	223 (94.09)	14 (5.91)	4.07 (0.56–22.76)	0.166
Other medical staff	57 (98.28)	1 (1.72)	0.49 (0.04– 5.83)	0.57
Office worker	47 (94.00)	1 (6.00)	ref.	–
Other non-medical staff	56 (100.00)	0 (0.00)	–	–
Workplace				
Hospital	141 (97.24)	4 (2.76)	ref.	–
Clinic	44 (91.67)	4 (8.33)	9.97 (1.53–64.81)	**0.016**
Long-term care health facility	300 (96.15)	12 (3.85)	0.44 (0.12–1.62)	0.22
Other	10 (100.00)	0 (0.00)	–	–

Table 3a
Comparison of participants' characteristics and IgG seropositive results in the rapid kit test or CLIA test in May and adjusted odds ratio for IgG seropositive results by gender, age, occupation, and workplace (n = 515).

	IgG (May)		Adjusted OR (95% CI) (n = 504)	*p* value
	Negative	Positive		
Gender				
Female	350 (91.38)	33 (8.62)	ref.	–
Male	125 (94.70)	7 (5.30)	0.69 (0.28–1.72)	0.43
Age				
18–44	246 (95.35)	12 (4.65)	ref.	–
45–64	195 (89.45)	23 (10.55)	2.25 (1.07–4.75)	**0.033**
65–78	34 (87.18)	5 (12.82)	2.85 (0.91–8.92)	0.072
Occupation				
Doctor	11 (100.00)	0 (0.00)	–	–
Nurse	93 (90.29)	10 (9.71)	1.03 (0.32–3.30)	0.97
Caregiver	219 (92.41)	18 (7.59)	0.77 (0.24–2.49)	0.66
Other medical staff	56 (96.55)	2 (3.45)	0.53 (0.09–3.08)	0.48
Office worker	45 (90.00)	5 (0.00)	ref.	–
Other non-medical staff	51 (91.07)	5 (8.93)	0.81 (0.21–3.07)	0.76
Workplace				
Hospital	136 (93.79)	9 (6.21)	ref.	–
Clinic	43 (89.58)	5 (10.42)	2.25 (0.68–7.47)	0.185
Long-term care health facility	287 (91.99)	25 (8.01)	1.34 (0.55–3.28)	0.53
Other	9 (90.00)	1 (10.00)	1.39 (0.15–13.06)	0.77

Table 3b
Comparison of participants' characteristics and IgG seropositive results in the rapid kit test or CLIA test in October and adjusted odds ratio for IgG seropositive results by gender, age, occupation, and workplace (n = 515).

	IgG (October)		Adjusted OR (95% CI) (n = 439)	*p* value
	Negative	Positive		
Gender				
Female	375 (97.91)	8 (2.09)	ref.	–
Male	129 (97.73)	3 (2.27)	1.60 (0.38–6.72)	0.52
Age				
18–44	256 (99.22)	2 (0.78)	ref.	–
45–64	210 (96.33)	8 (3.67)	4.42 (0.91–21.40)	0.065
65–78	38 (97.44)	1 (2.56)	2.78 (0.23–33.54)	0.42
Occupation				
Doctor	11 (100.00)	0 (0.00)	–	–
Nurse	99 (96.12)	4 (3.88)	1.16 (0.18–7.35)	0.88
Caregiver	233 (98.31)	4 (1.69)	0.48 (0.07–3.48)	0.47
Other medical staff	58 (100.00)	0 (0.00)	–	–
Office worker	48 (96.00)	2 (4.00)	ref.	–
Other non-medical staff	55 (98.21)	1 (1.79)	0.37 (0.03–4.54)	0.44
Workplace				
Hospital	141 (97.24)	4 (2.76)	ref.	–
Clinic	47 (97.92)	1 (2.08)	1.01 (0.10–10.58)	0.99
Long-term care health facility	306 (98.08)	6 (1.92)	0.81 (0.19–3.54)	0.78
Other	10 (100.00)	0 (0.00)	–	–

(a) IgM

Patient	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45
Rapid kit test in May																																													
CLIA in May	0.35	3.55	0.47	0.49	2.58	1	0.44	5.53	5.41	0.34	2.74	7.11	1.06	1.76	3.09	5.61	1.21	0.23	1.94	1.5	1.98	2.67	1.19	1.08	1.36	3.78	0.65	0.77	61.2	4.6	0.34	3.71	1.08	0.26	2.94	1.47	6.48	6.17	6.45	1.48	0.41	0.36	0.43	1.84	1.32
Rapid kit test in October																																													
CLIA in October	0.33	1.44	0.23	0.25	1.23	0.49	0.31	3.99	3.21	0.27	1.54	4.94	0.55	0.84	1.46	3.17	1.02	0.21	0.72	0.78	1.32	1.16	0.52	0.54	0.96	1.59	0.39	0.42	95.6	2.72	0.25	1.87	0.44	0.22	1.97	0.75	11.7	0.59	1.61	0.88	0.25	0.33	1.09	1.12	0.71
Date of PCR	May-20	Jun-20	Jun-20	May-20	May-20	May-20	Jun-20	May-20	May-20	May-20	May-20	May-20	May-20	May-20	May-20	Aug-20	May-20	May-20	-	May-20	May-20	-	Jun-20	May-20	May-20	May-20	May-20	Aug-20	Aug-20	Aug-20	Aug-20	May-20	May-20	May-20	May-20	-	-	May-20	May-20	Jun-20	May-20	May-20	May-20	May-20	May-20
Fever in 2020 Jan–Oct																																												

(b) IgG

Patient	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40				
Rapid kit test in May																																											Positive
CLIA in May	7.63	0.18	0.78	0.65	2.39	3.82	11.2	0.32	11.1	0.63	0.9	4.36	0.36	21.8	1.33	3.49	7.11	2.46	1.05	0.33	1.89	1.2	1.72	4.03	12.7	21.7	3.75	1.05	0.55	0.75	0.52	1.65	2.13	1.76	6.9	1.24	2.81	4.2	0.18	5.5				Negative
Rapid kit test in October																																												
CLIA in October	5	0.1	0.47	0.46	1.28	1.19	5.16	0.19	7.96	0.39	0.34	2.42	0.21	16.3	0.6	3.34	1.75	0.7	0.47	0.16	0.8	0.97	1.08	3.06	3.02	11.4	1.04	0.81	0.25	0.38	0.28	0.95	1.09	0.95	4.24	0.4	2.13	3.29	0.1	3.26				
Date of PCR	Oct-21	-	May-21	Sep-20	-	-	May-20	-	May-20	-	May-20	Oct-21	-	Dec-19	Apr-19	-	-	May-20	-	May-20	-	May-20	Oct-21	-	Jul-18	Oct-17	-	-	May-20	-	May-20	-	May-20	Oct-21	-	Feb-17	May-16	-	-	May-20				
Fever in 2020 Jan–Oct																																											

Fig. 2. The summary of the seroprevalence of each assay and each term and complaints of fever. A; IgM, B; IgG. The cut-off value of this chemiluminescence immunoassay quantitative antibody test is 10AU/ml. CLIA = Chemiluminescence immunoassay. PCR = Polymerase chain reaction.

from 7.77% in May to 2.14% in October. The proportions of seropositive prevalence in the CLIA were compared with the number of confirmed cases in the Central Fukushima area between March and November and found to be consistent.

The results of completely seropositive participants in at least one antibody assay were summarized in Fig. 2 for IgM and IgG, respectively. However, the majority of participants who were seropositive in May became seronegative in October. Moreover, a few patients had fever from January 2020 till the day of the second examination. Nevertheless, no participant had COVID-19 according to the PCR test.

The numerical value of the CLIA in May for each of the ten groups was obtained until October. The median value of each group in October decreased in almost all groups as compared to that in May. The overall median value significantly decreased from the first survey to the second survey for IgG than for IgM. Forty-nine individuals had increased IgM values in the CLIA, and three individuals had increased IgG values in the CLIA (Supplementary Table 1). Moreover, the proportions of seropositive prevalence in the CLIA in each term were found to be consistent with the number of confirmed COVID-19 cases in Central Fukushima rather than the total number of confirmed cases in the entire Fukushima Prefecture (Supplementary Fig. 1).

4. Discussion

A follow-up antibody survey for COVID-19 is vital for understanding cohort-based infection status and infection control decision-making. The present study aimed to investigate the consecutive changes in COVID-19 antibody prevalence among hospital staff in the rural parts of Central Fukushima.

The IgG and IgM antibody seroprevalence among hospital staff in rural Central Fukushima decreased, which was consistent with the number of confirmed COVID-19 cases in the area during the period of testing and pre-testing. The number of individuals with over cutoff values for IgM in the CLIA increased from one to two individuals, yet the number of seropositive individuals for IgG in the CLIA clearly decreased, as they did for the rapid kit test for both IgM and IgG. The antibody values changed in the follow-up survey in the population that was not identified as having the infection using PCR. However, it was generally reported that IgG does not decrease, while IgM greatly decreases in patients who recover from COVID-19 in a previous study [16,17]. Nevertheless, both IgG and IgM seroprevalence decreased in this study's cohorts; thus, the results differed from those of a study conducted in cohorts recovered from COVID-19 [16]. However, a decrease of IgG antibodies in the rapid test has been revealed in previous studies [18]. Previous studies have shown that the proportion of antibody decrease was higher among patients with milder symptoms than those with severe symptoms [19]. In this study, we examined uninfected participants using the PCR test, for whom the change of antibodies might be different from that of hospitalized patients. Further research is required to understand the reasons for this result. However, the follow-up antibody testing was useful in understanding the status of seroprevalence among hospital staff to confirm that antibody titers did not increase in a hospital covering a large rural area in Central Fukushima.

Meanwhile, there was also a discrepancy between the results of the CLIA and the rapid kit test, and this trend was clear for IgM. A large discrepancy was observed in the first test as well as the second test. These discrepancies have been observed in many previous studies [20–23]. Such results can sometimes confuse the community and cause mental stress in individuals. Nevertheless, in the present study, a low prior probability of COVID-19 testing in the target cohort might have caused false positives, and these characteristics of antibody assays should be widely recognized among hospital staff.

The characteristics of IgM and IgG seropositive groups among hospital staff were different across the survey periods. Seroprevalence of IgM and IgG was higher in the aging group in May, yet this trend was not observed in October. Further, the seroprevalence of IgM was higher in the female group. The seroprevalence was not higher in older groups in a previous study among hospital staff, [6,24] and the age groups with a high seroprevalence of antibodies were different among surveys [4,25]. The seroprevalence of IgM was not higher in the female group in a previous study as well [24,25]. Continuing further testing in the same cohort may help in understanding the cause. Additionally, further consecutive surveys on antibody prevalence among the population without symptoms and false-positive patients are required.

Antibody follow-up testing among hospital staff in the hospital covered a wide range of rural residents and helped to reassure anxious staff. The seropositive proportion was higher than expected in the baseline survey, and consequently, the staff had to manage confirmation tests and increased anxiety. However, in the follow-up test, most of the staff had a better understanding of the antibody assay characteristics; thus, there was less confusion among the hospital staff. In addition, the antibody low seroprevalence made the staff aware that their routine measures against COVID-19 were in the right direction. The number of hospitals is usually limited in rural areas, and one hospital covers patients from a wide area. In such a setting, constant testing for antibody titers among hospital staff was useful in confirming the correctness of the measures they were taking, in estimating the COVID-19 infection status among hospital staff, and in reassuring the staff when the antibody positivity rate began decreasing. Thus, conducting follow-up antibody testing among the hospital staff cohort in addition to routine infection control measures had several merits.

Nevertheless, several limitations should be considered when

interpreting these findings. First, the prevalence of COVID-19 patients was low in the research area; thus, seropositive antibody assays might not be reliable. Second, the possibility of cross-reactions was not considered when assessing the seropositive results of each test. Third, conducting two testing procedures might have affected the laboratory technologist's judgment of seropositive results. The technologists knew that there were many false positives in the baseline test, which might have influenced their judgment in the follow-up survey. Fourth, in the present study, we could not explain the differences in the participants characteristics between the IgM and IgG across the survey periods Further studies will be required to identify the reason for the differences. Fifth, the results of the rapid kit test and CLIA test, differed greatly, which made it difficult to interpret the results. Finally, the interpretation of the different result among two tests were not determined. We could not determine the definition in this study as well. This require further discussion and research. Despite these limitations, this study was one of the largest sample size studies that followed up on antibody testing results among hospital staff.

5. Conclusion

The present study surveyed consecutive antibody seroprevalence of SARS-CoV-2 among hospital staff in a hospital, covering a wide area with rural residents. Subsequently, it was found that the seroprevalence among hospital staff decreased, which was consistent with the number of confirmed COVID-19 cases in the Central Fukushima area. Although it is difficult to interpret the results of antibody assays in a population with a low prior probability, constant follow-up surveys of antibody titers among hospital staff had several merits in obtaining a set of criteria on the correctness of the measures against COVID-19 and in estimating the infection status of COVID-19 among hospital staff.

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Declaration of Competing Interest

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

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Appendix A. Supplementary data

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References

[1] E. Kritsotakis, On the importance of population-based serological surveys of SARS-CoV-2 without overlooking their inherent uncertainties, Public Health Pract. 1 (2020), 100013, https://doi.org/10.1016/j.puhip.2020.100013.

[2] M. Pollán, B. Pérez-Gómez, R. Pastor-Barriuso, J. Oteo, M.A. Hernán, M. Pérez-Olmeda, J.L. Sanmartín, A. Fernández-García, I. Cruz, N. Fernández de Larrea, M. Molina, F. Rodríguez-Cabrera, M. Martín, P. Merino-Amador, J. León Paniagua, J.F. Muñoz-Montalvo, F. Blanco, R. Yotti, ENE-COVID Study Group. Prevalence of SARS-CoV-2 in Spain (ENE-COVID): a nationwide, population-based seroepidemiological study, Lancet 396 (2020) 535–544, https://doi.org/10.1016/S0140-6736(20)31483-5.

[3] H. Ho, F. Wang, H. Lee, Y. Huang, C. Lai, W. Jen, S.-L. Hsieh, T.-Y. Chou, Seroprevalence of COVID-19 in Taiwan revealed by testing anti-SARS-CoV-2 serological antibodies on 14,765 hospital patients, Lancet Reg. Health West. Pac. 3 (2020), 100041, https://doi.org/10.1016/j.lanwpc.2020.100041.

[4] S. Stringhini, A. Wisniak, G. Piumatti, A.S. Azman, S.A. Lauer, H. Baysson, D. de Ridder, D. Petrovic, S. Schrempft, K. Marcus, S. Yerly, I.A. Vernez, O. Keiser, S. Hurst, K.M. Posfay-Barbe, D. Trono, D. Pittet, L. Gétaz, F. Chappuis, I. Eckerle, N. Vuilleumier, B. Meyer, A. Flahault, L. Kaiser, I. Guessous, Seroprevalence of anti-SARS-CoV-2 IgG antibodies in Geneva, Switzerland (SEROCoV-POP): a population-based study, Lancet 396 (2020) 313–319, https://doi.org/10.1016/S0140-6736(20)31304-0.

[5] K. Macartney, H.E. Quinn, A.J. Pillsbury, A. Koirala, L. Deng, N. Winkler, A.L. Katelaris, M.V.N. O'Sullivan 6, C. Dalton, N. Wood, N.S.W. COVID-19 Schools Study Team. Transmission of SARS-CoV-2 in Australian educational settings: a prospective cohort study, Lancet Child Adolesc. Health. 4 (2020) 807–816. https://doi.org/10.1016/S2352-4642(20)30251-0.

[6] K. Iversen, H. Bundgaard, R.B. Hasselbalch, J.H. Kristensen, P.B. Nielsen, M. Pries-Heje, A.D. Knudsen, C.E. Christensen, K. Fogh, J.B. Norsk, O. Andersen, T. K. Fischer, C.A.J. Jensen, M. Larsen, C. Torp-Pedersen, J. Rungby, S.B. Ditlev, I. Hageman, R. Møgelvang, C.E. Hother, M. Gybel-Brask, E. Sørensen, L. Harritshøj, F. Folke, C. Sten, T. Benfield, S.D. Nielsen, H. Ullum, Risk of COVID-19 in healthcare workers in Denmark: an observational cohort study, Lancet Infect Dis. 20 (2020) 1401–1408, https://doi.org/10.1016/S1473-3099(20)30589-2.

[7] S.C. Pan, Y.S. Huang, S.M. Hsieh, Y.C. Chen, S.Y. Chang, S.C. Chang. A cross-sectional seroprevalence for COVID-19 among healthcare workers in a tertially care hospital in Taiwan, J Formos Med. Assoc. (2021) S0929-6646(21)00019-X. Epub ahead of print. https://doi.org/10.1016/j.jfma.2021.01.002.

[8] B.R. Hunter, L. Dbeibo, C.S. Weaver, C. Beeler, M. Saysana, M.K. Zimmerman, L. Weaver. Seroprevalence of severe acute respiratory coronavirus virus 2 (SARS-CoV-2) antibodies among healthcare workers with differing levels of coronavirus disease 2019 (COVID-19) patient exposure, Infect. Control Hosp. Epidemiol. 41 (2020) 1441–1442. https://doi.org/10.1017/ice.2020.390.

[9] C.F. Houlihan, N. Vora, T. Byrne, D. Lewer, G. Kelly, J. Heaney, S. Gandhi, M.J. Spyer, R. Beale, P. Cherepanov, D. Moore, R. Gilson, S. Gamblin, G. Kassiotis, L.E. McCoy, C. Swanton, Crick COVID-19 Consortium, A. Hayward, E. Nastouli, SAFER Investigators, Pandemic peak SARS-CoV-2 infection and seroconversion rates in London frontline health-care workers, Lancet 396 (2020) e6–e7, https://doi.org/10.1016/S0140-6736(20)31484-7.

[10] S. Ochi, M. Tsubokura, S. Kato, S. Iwamoto, S. Ogata, T. Morita, A. Hori, T. Oikawa, A. Kikuchi, Z. Watanabe, Y. Kanazawa, H. Kumakawa, Y. Kuma, T. Kumakura, Y. Inomata, M. Kami, R. Shineha, Y. Saito, Hospital staff shortage after the 2011 triple disaster in Fukushima, Japan-an earthquake, tsunamis, and nuclear power plant accident: a case of the Soso District, PloS One. 11 (2016), e0164952, https://doi.org/10.1371/journal.pone.0164952.

[11] Y. Nishikawa, M. Tsubokura, Y. Takahashi, S. Nomura, A. Ozaki, Y. Kimura, T. Morita, T. Sawano, T. Oikawa, T. Nakayama, Change of access to emergency care in a repopulated village after the 2011 Fukushima nuclear disaster: a retrospective observational study, BMJ Open. 9 (2019), e023836, https://doi.org/10.1136/bmjopen-2018-023836.

[12] K. Fujita, S. Kada, O. Kanai, H. Hata, T. Odagaki, N. Satoh-Asahara, T. Tagami, A. Yasoda, Quantitative SARS-CoV-2 antibody screening of healthcare workers in the southern part of Kyoto City during the COVID-19 pre-pandemic period, Front Public Health. 8 (2020), 595348, https://doi.org/10.3389/fpubh.2020.595348.

[13] Y. Kobashi, Y. Shimazu, Y. Nishikawa, T. Kawamura, T. Kodama, D. Obara, M. Tsubokura, The difference between IgM and IgG antibody prevalence in different serological assays for COVID-19; lessons from the examination of healthcare workers, Int Immunopharmacol. 92 (2021), 107360, https://doi.org/10.1016/j.intimp.2020.107360.

[14] Vazyme, 2019-nCoV IgG / IgM Detection Kit (Colloidal Gold-Based) Instructions for Use (Version 2.0). https://mtendoscopy.com/wp-content/uploads/2020/04/Vazyme_2019-nCoV-IgG-IgM-Detection-Kit-Instruction-for-Use04.28.20-Final.pdf, 2020 (accessed 7 May 2021).

[15] Roche Molecular Systems I, LightCycler® 480 Instrument II. https://lifescience.roche.com/global_en/products/lightcycler14301-480-instrument-ii.html, 2020 (accessed 7 February 2021).

[16] C. Huang, L. Huang, Y. Wang, X. Li, L. Ren, X. Gu, L. Kang, L. Guo, M. Liu, X. Zhou, J. Luo, Z. Huang, S. Tu, Y. Zhao, L. Chen, D. Xu, Y. Li, C. Li, L. Peng, Y. Li, W. Xie, D. Cui, L. Shang, G. Fan, J. Xu, G. Wang, Y. Wang, J. Zhong, C. Wang, J. Wang, D. Zhang, B. Cao, 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study, Lancet 397 (2021) 220–232, https://doi.org/10.1016/S0140-6736(20)32656-8.

[17] M. Rashid-Abdi, A. Krifors, A. Sälléber, J. Eriksson, E. Månsson, Low rate of COVID-19 seroconversion in health-care workers at a Department of Infectious Diseases in Sweden during the later phase of the first wave; a prospective longitudinal seroepidemiological study, Infect Dis (Lond). 53 (2021) 169–175.

[18] A. Mostafa, S. Kandil, M.H. El-Sayed, S. Girgis, H. Hafez, M. Yosef, S. Saber, H. Ezzelarab, M. Ramadan, E. Algohary, G. Fahmy, I. Afifi, F. Hassan, S. Elsayed, A. Reda, D. Fattuh, A. Mahmoud, A. Mansour, M. Sabry, P. Habeb, F.S. Ebeid, A. Elanwar, A. Saleh, O. Mansour, A. Omar, M. El-Meteini, SARS-CoV-2 seroconversion among 4040 Egyptian healthcare workers in 12 resource-limited healthcare facilities: A prospective cohort study, Int J Infect Dis. 104 (2021) 534–542.

[19] J. Van Elslande, M. Oyaert, S. Ailliet, M. Van Ranst, N. Lorent, Y. Vande Weygaerde, E. André, K. Lagrou, S. Vandendriessche, P. Vermeersch, Longitudinal follow-up of IgG anti-nucleocapsid antibodies in SARS-CoV-2 infected patients up to eight months after infection, J. Clin. Virol. 136 (2021), 104765.

[20] T. Yoshiyama, Y. Saito, K. Masuda, Y. Nakanishi, Y. Kido, K. Uchimura, S. Mitarai, T. Suzuki, Y. Nakagama, H. Kubota, M. Satomi, S. Uchikoba, M. Ohnishi, T. Wakita, S. Kato, K. Kato, Prevalence of SARS-CoV-2-specific antibodies, Japan, Emerg. Infect. Dis. 27 (2021) (June 2020) 628–631, https://doi.org/10.3201/eid2702.204088.

[21] I. Montesinos, D. Gruson, B. Kabamba, H. Dahma, S. van den Wijngaert, S. Reza, V. Carbone, O. Vandenberg, B. Gulbis, F. Wolff, H. Rodriguez-Villalobos, Evaluation of two automated and three rapid lateral flow immunoassays for the detection of anti-SARS-CoV-2 antibodies, J Clin. Virol. 128 (2020), 104413, https://doi.org/10.1016/j.jcv.2020.104413.

[22] M. Plebani, A. Padoan, D. Negrini, B. Carpinteri, L. Sciacovelli, Diagnostic performances and thresholds: The key to harmonization in serological SARS-CoV-2 assays? Clin. Chim. Acta. 509 (2020) 1–7, https://doi.org/10.1016/j.cca.2020.05.050.

[23] B. Flower, J.C. Brown, B. Simmons, M. Moshe, R. Frise, R. Penn, R. Kugathasan, C. Petersen, A. Daunt, D. Ashby, S. Riley, C.J. Atchison, G.P. Taylor, S. Satkunarajah, L. Naar, R. Klaber, A. Badhan, C. Rosadas, M. Khan, N. Fernandez, M. Sureda-Vives, H.M. Cheeseman, J. O'Hara, G. Fontana, S.J.C. Pallett, M. Rayment, R. Jones, L.S.P. Moore, M.O. McClure, P. Cherepanov, R. Tedder, H. Ashrafian, R. Shattock, H. Ward, A. Darzi, P. Elliot, W.S. Barclay, G.S. Cooke, Clinical and laboratory evaluation of SARS-CoV-2 lateral flow assays for use in a national COVID-19 seroprevalence survey, Thorax 75 (2020) 1082–1088, https://doi.org/10.1136/thoraxjnl-2020-215732.

[24] D. Steensels, E. Oris, L. Coninx, D. Nuyens, M.L. Delforge, P. Vermeersch, L. Heylen, Hospital-wide SARS-CoV-2 antibody screening in 3056 staff in a tertiary center in Belgium, JAMA 324 (2020) 195–197, https://doi.org/10.1001/jama.2020.11160.

[25] M. Takita, T. Matsumura, K. Yamamoto, E. Yamashita, K. Hosoda, T. Hamaki, E. Kusumi, Geographical profiles of COVID-19 outbreak in Tokyo: an analysis of the primary care clinic-based point-of-care antibody testing, 2150132720942695, J Prim. Care Community Health. 11 (2020), https://doi.org/10.1177/2150132720942695.