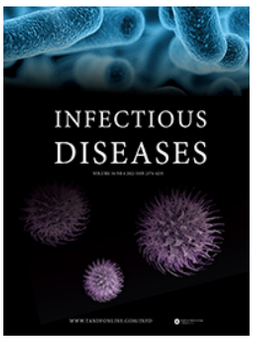

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BRIEF REPORT

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Low pre-vaccination SARS-CoV-2 seroprevalence in Finnish health care workers: a prospective cohort study

Paula A. Tähtinen[a*], Lauri Ivaska[a*], Pinja Jalkanen[b], Laura Kakkola[b], Leena Kainulainen[a], Jukka Hytönen[b,c], Tytti Vuorinen[b,c], Matti Waris[b,c], Ville Peltola[a], Jarmo Oksi[d], Ilkka Julkunen[b,c†] and Johanna Lempainen[a,c,e†]

[a]Department of Paediatrics and Adolescent Medicine, Turku University Hospital and University of Turku, Turku, Finland; [b]Infections and Immunity Unit, Institute of Biomedicine, University of Turku, Turku, Finland; [c]Clinical Microbiology Division, Turku University Hospital, Turku, Finland; [d]Department of Infectious Diseases, Turku University Hospital and University of Turku, Turku, Finland; [e]Immunogenetics Laboratory, Institute of Biomedicine, University of Turku, Turku, Finland

ABSTRACT

Background: Health care workers are at risk of acquiring SARS-CoV-2 infection. Our aim was to study the prevalence of SARS-CoV-2 nucleoprotein and spike protein specific antibodies in health care workers with occupational exposure to COVID-19 in Turku, Finland, from May to December 2020.

Methods: Health care workers of Turku University Hospital units caring for COVID-19 patients or handling clinical SARS-CoV-2 samples were invited to participate in the study. The presence of SARS-CoV-2 nucleoprotein and spike protein specific IgG antibodies were analysed with in-house enzyme immunoassay.

Results: At study enrolment, only one of the 222 (0.5%) study participants was seropositive for SARS-CoV-2 protein specific antibodies. Two additional study participants (2/222, 0.9%) seroconverted during the follow-up. All these participants were diagnosed with a RT-PCR-positive COVID-19 infection before turning seropositive.

Conclusion: In our study population, the prevalence of SARS-CoV-2 seropositivity remained low. The absence of seropositive cases without previous RT-PCR confirmed infections demonstrate good access to diagnostics. In addition to high vaccine coverage, high standards of infection prevention practices and use of standard personal protective equipment seem sufficient in preventing occupational SARS-CoV-2 infection in a setting with low number of circulating virus. However, it remains unclear whether similar protective practices would also be effective against more transmissible SARS-CoV-2 variants.

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CONTACT
Paula A. Tähtinen
paula.tahtinen@utu.fi
Department of Paediatrics and Adolescent Medicine, Turku University Hospital, Kiinamyllynkatu 4–8, Turku 20520, Finland

*Paula A. Tähtinen and Lauri Ivaska contributed equally to this work.
†Ilkka Julkunen and Johanna Lempainen contributed equally to this work.

Introduction

During the ongoing pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), increased risk of infection in front-line health care workers (HCWs) has been suggested [1–5]. Recent serosurveys have enabled more accurate estimation of the true burden of infections in occupational settings. Based on these data, standard infection precautions seem effective in preventing the spread of SARS-CoV-2 in health care [6,7].

In comparison with many European countries, the burden of coronavirus disease 2019 (COVID-19) has remained low in Finland throughout the pandemic [8]. In 2020, the greatest surges in COVID-19 related hospital admission rates in Finland occurred in April-May and again in November-December [9]. In Turku University Hospital, infection prevention practices included personal protective equipment (PPE) for droplet precautions in all suspected or confirmed SARS-CoV-2 cases and for airborne precautions during aerosol generating procedures. Symptomatic health care workers had easy access to SARS-CoV-2 PCR testing as part of the local public health policy. In a setting where SARS-CoV-2 circulation in the community remains low, occupational exposure to the virus could increase the infection risk among HCWs substantially.

The aim of this study was to evaluate the prevalence of SARS-CoV-2-specific antibodies among the front-line HCWs at Turku University Hospital, in Turku, Finland, and their occupational risk for COVID-19 infection.

Materials and methods

Study participants and setting

In May 2020, HCWs (doctors, nurses) of Turku University Hospital units caring for COVID-19 patients or handling clinical SARS-CoV-2 samples were invited to participate in the study. The recruitment continued until December 2020, when SARS-CoV-2 vaccination started in Finland. Clinical care of COVID-19 patients in the Turku University Hospital was organised as follows: Outpatients with any symptoms suggestive of an infection were cohorted in the emergency department and evaluated in isolation from other patients. Those who were admitted to hospital were taken care of in the intensive care unit, adult infectious diseases or pulmonology wards, or paediatric wards depending on the clinical context. All the above-mentioned units served as mixed wards providing treatment to other than COVID-19 patients as well. In addition to clinical staff, laboratory staff working in the units operating with testing, handling, or analysing the clinical SARS-CoV-2 samples was invited to participate in the study.

Exclusion criterion was intravenous immunoglobulin treatment within previous 6 months. The study protocol was approved by the Ethics Committee of the Hospital District of Southwest Finland. All participants provided written informed consent.

Follow-up

At enrolment, all participants filled a detailed background and symptom questionnaire. Repeated serum samples were collected and symptom questionnaires filled out every 2–3 months. For this analysis, sampling times were divided into three time points: May-July, August-October, and November-December 2020. The participants were encouraged to have a reverse transcription polymerase chain reaction (RT-PCR) test for SARS-CoV-2 taken whenever they had symptoms suggestive of COVID-19 infection. RT-PCR tests were arranged as part of local infection control practice.

Serological assays

The presence of SARS-CoV-2 nucleoprotein (N) and spike protein (S1) specific IgG antibodies were analysed with enzyme immunoassay (EIA) as described previously [10]. Briefly, serum samples diluted 1:300 in PBS supplemented with 5% swine serum (Biological Industries) and 0.1% Tween20 were incubated in 96-well plates precoated with purified recombinant SARS-CoV-2 N (2.0 μg/ml) and S1 proteins (3.0 μg/ml) for 2 h at +37 °C. SARS-CoV-2 specific antibodies were detected with HRP conjugated anti-human IgG antibodies (1:8000 dilution, Dako) and TMB One substrate (Kementec Solutions). The absorbance was measured at 450 nm wavelength and optical density (OD) values were converted into EIA units using linear interpolation between positive control (100 EIA units) and negative control (0 EIA units) OD values. Unlike in the previous study, the absorbance of negative control antigens was not measured. A sample was considered SARS-CoV-2 seropositive if both anti-S1 and anti-N IgG antibody levels exceeded the cut-off values that were determined with the same samples and receiver operating characteristics curve as in the previous study [10]. The cut-off value for anti-S1 antibody was 15 and for anti-N 11 EIA units.

Table 1. Clinical characteristics of the 222 study participants.

Characteristic	
	Median [IQR]
Age (years)	39.6 [32.3–48.1]
	No. (%)
Gender	
Female	204 (91.9)
Male	18 (8.1)
Primary working unit	
Emergency department	28 (12.6)
Intensive care unit	38 (17.1)
Infectious diseases	24 (10.8)
Pulmonology	22 (9.9)
Paediatrics	65 (29.3)
Clinical microbiology	45 (20.3)
Profession	
Physician	32 (14.4)
Registered nurse	132 (59.5)
Practical nurse	13 (5.9)
Laboratory personnel	45 (20.3)
Travelled abroad in 2020	63 (28.4)
Number of other household members	
0	46 (20.7)
1–2	108 (48.6)
3–4	58 (26.1)
≥5	10 (4.5)
Any respiratory tract infection before study enrolment in 2020	138 (62.2)
RT-PCR confirmed COVID-19-infection before study enrolment	4 (1.8)
Contact with a SARS-CoV-2-positive patient at work with personal protective equipment	114 (51.4)
Contact with a SARS-CoV-2-positive person without adequate protection	15 (6.8)
At work (patient)	7 (3.2)
At work (coworker)	2 (0.9)
At home (household member)	1 (0.5)
Other	5 (2.3)
COVID-19-infection during follow-up (RT-PCR-positive)[a]	2 (0.9)

IQR: interquartile range; COVID-19: coronavirus disease; RT-PCR: reverse transcription polymerase chain reaction; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.
[a]Between study enrolment and 17 December 2020.
All the other characteristics are reported at study enrolment.

Results

Between 13 May 2020 and 17 December 2020, before SARS-CoV-2 vaccination started in Finland, 222 HCWs provided written informed consent, returned the background information questionnaire, and had at least one serum sample collected for SARS-CoV-2 antibody measurement. Median age of the study participants was 39.6 years, 204 (91.9%) were females and 132 (59.5%) of them worked as registered nurses. The demographics of the study participants are presented in Table 1. The recruitment continued through the whole study period and 158/222 (71.2%) of the study participants were recruited by the beginning of July 2020. Repeated serum samples were collected and symptom questionnaires filled out every 2–3 months. By the end of 2020, 2 or more blood samples were available for testing from 191/222 (86.0%) of the study participants.

In 2020 before enrolment in the study, 138/222 (62.2%) of participants had at least one respiratory tract infection but only 4/222 (1.8%) reported a positive SARS-CoV-2 RT-PCR test result (Table 1). One of the four PCR-positive participants had SARS-CoV-2 S1 and N specific antibodies in the first serum sample collected 104 days after the positive RT-PCR test result (Figure 1). Thus, the seropositivity rate for SARS-CoV-2 S1 and N proteins was 0.5% (1/222) at study enrolment. Other three PCR-positive participants were N and S1 seronegative at the time of the first serum sample collection 53–98 days after their positive RT-PCR test result. All of the three seronegative participants had mild symptoms during their illness (Table 2). During the follow-up, two additional study participants (2/222, 0.9%) tested positive for SARS-CoV-2 by RT-PCR, and both of the participants expressed anti-N and anti-S1 antibodies 20 and 38 days after the positive RT-PCR test result in December 2020 (Figure 1). Only one study participant with RT-PCR-positive COVID-19 was treated in a hospital. Personal contact with SARS-CoV-2 positive patients or samples while using PPE was reported by 114/222 (51.4%) participants at study enrolment. During the study period (13 May to 17 December 2020), 80 patients were treated in the Turku University Hospital due to COVID-19 infection.

Antibodies only against SARS-CoV-2 N protein were detected in 14/222 (6.3%) participants (Figure 1). One participant (1/222, 0.5%) had antibodies only against

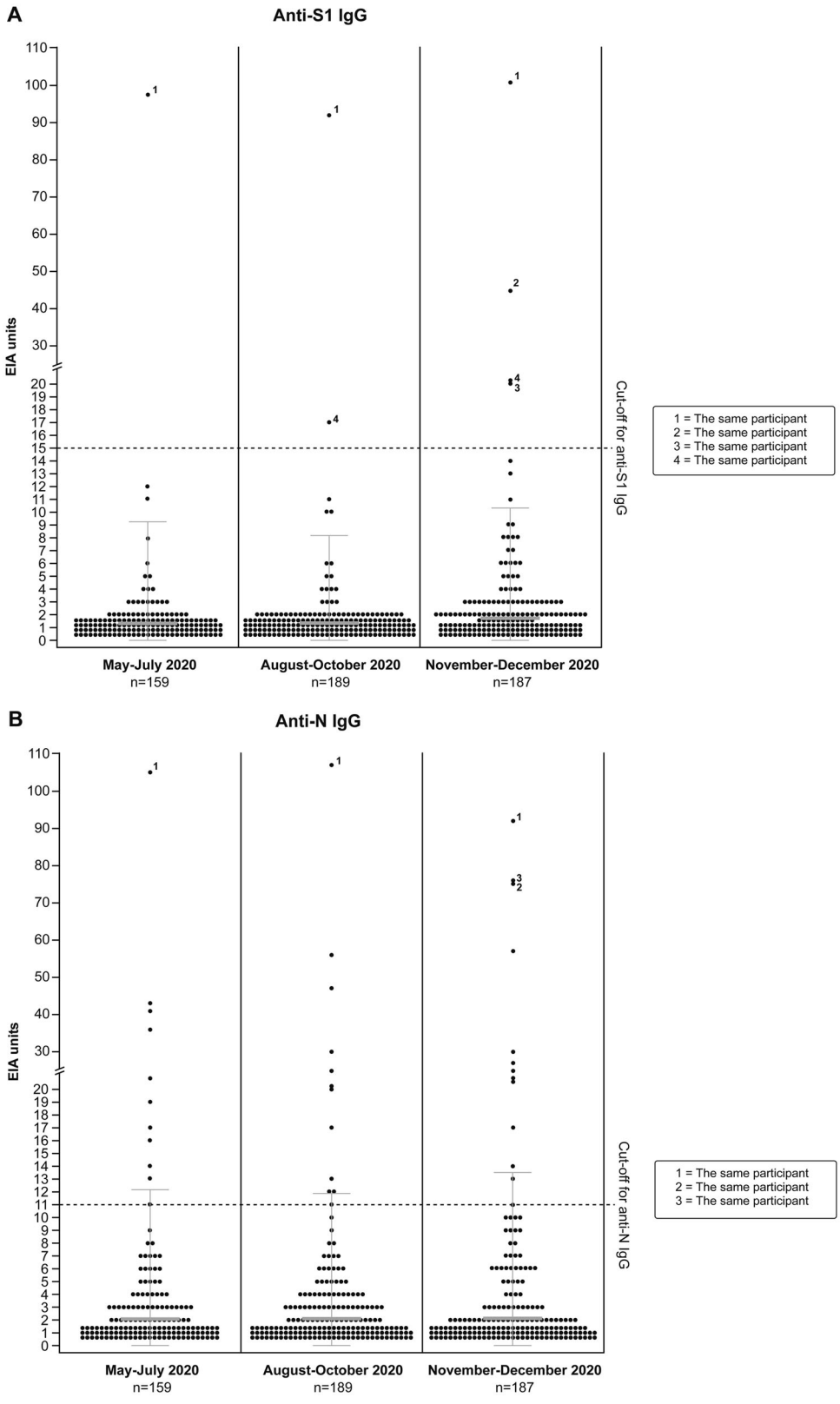

Figure 1. Antibody responses against SARS-CoV-2 S1 and N proteins during follow-up.
IgG antibody levels against SARS-CoV-2 spike protein S1 domain (panel A) and nucleoprotein N (panel B) were analysed with enzyme immunoassay (EIA) [10]. The cut off-value for anti-S1 IgG was 15 EIA units and for anti-N IgG 11 EIA units. The sample was considered SARS-CoV-2 seropositive if both anti-S1 and anti-N IgG antibody levels were above the respective cut-off values. Three participants had both, anti-S1 IgG and anti-N IgG antibodies (numbered as 1–3), one participant had only anti-S1 IgG antibodies (numbered as 4), and 14 participants had only anti-N IgG antibodies. The figure shows the EIA unit values (black dots) of serum specimen collected at indicated times of the follow-up. The geometric means and standard deviations of means are shown.

Table 2. Clinical details of study participants ($n = 6$) with PCR-positive COVID-19-infection.

Study participant	SARS-CoV-2 RT-PCR cycle threshold	Serology[a]	Treated in hospital	Contact with a SARS-CoV-2 -positive person without adequate protection	Contact with a SARS-CoV-2 -positive patient at work with personal protective equipment	Associated symptoms
COVID-19-infection before study enrolment (PCR-positive)						
1	38.9	Neg	No	No	No	Myalgia, fatigue, lack of appetite
2	38.2	Pos	Yes	No	Yes	Fever, severe cough, fatigue, dyspnoea, headache, rhinitis, vomiting
3	41.7	Neg	No	No	No	Dyspnoea, loss of smell, loss of taste, arthralgia
4	16.7	Neg	No	Yes[b]	Yes	Rhinitis, loss of smell, loss of taste
COVID-19-infection during follow-up (PCR-positive)						
5	26.8	Pos	No	No	Yes	Fatigue, headache, loss of smell, loss of taste, nasal irritation
6	19.8	Pos	No	No	Yes	Fever, severe cough, fatigue, sore throat, loss of smell, loss of taste, rhinitis, myalgia

[a]SARS-CoV-2 S1 and N protein specific antibodies.
[b]Household contact.

SARS-CoV-2 S1 protein (Figure 1). Of the 14 anti-N seropositive participants, seven had anti-N antibodies in all of the follow-up serum samples collected 3–7 months from the first serum sample and two had anti-N antibodies in the only serum sample collected. Two had anti-N antibodies at enrolment, but became seronegative during follow-up. However, three participants had one anti-N IgG positive sample in the middle of the follow up period indicating discrepancies in measuring only N-protein specific antibodies.

The three seropositive participants (anti-S1 and anti-N) worked at the intensive care unit, adult infectious diseases, and pulmonology wards, and they all had taken care of COVID-19 patient by wearing PPE before they tested positive for SARS-CoV-2 by RT-PCR. None of the seropositive study participants reported of being in contact with SARS-CoV-2 positive persons, at work or at home, without PPE prior to their infection (Table 2). None of the laboratory personnel became seropositive during the follow-up.

Discussion

The results of this prospective cohort study in HCWs at Turku University Hospital, Finland, suggest a low occupational risk of COVID-19 -infection. The low rate of seropositivity in this population reflects the low level of SARS-CoV-2 transmission in the community.

Our data with frequent occupational exposure to SARS-CoV-2 and low rate of seropositivity confirm the earlier findings that high quality of infection control measures, including standard PPE, seem effective in preventing COVID-19 -infection at the hospital environment [6,7]. In this respect, the efforts that are targeted against the spread of the pandemic in the community are the key elements of preventing transmission in the HCWs as well. It remains unclear whether similar protective practices in hospital would also be effective against highly transmissible SARS-CoV-2 alpha (B.1.1.7), delta (B.1.617.2), and omicron (B.1.1.529) variants. Another important element in reducing the transmission of the virus is the accessibility to SARS-CoV-2 diagnostic testing. Part of the local public health policy was that the symptomatic health care workers had easy access to SARS-CoV-2 PCR testing. In our data, RT-PCR-positive COVID-19 was more common than seropositivity for both SARS-CoV-2 S and N specific antibodies. Furthermore, there were no seropositive cases without prior microbiologically confirmed COVID-19 -infection. However, regular testing of asymptomatic health care workers was not in place during any period of the pandemic.

Limitations of this study include the relatively small number of participants, single-center design and the lack of control cohort working in a non-hospital environment. Since the number of SARS-CoV-2 anti-S1 and anti-N seropositivity was low, we were unable to calculate specific risks for different types of occupational exposures. In all of the three seropositive cases, the source of the infection could not be verified and, therefore, the transmission SARS-CoV-2 at the occupational setting could not be excluded. Data collection for this study was terminated on the 17th of December 2020 since vaccination of HCWs against SARS-CoV-2 started soon after and the effects of vaccine-induced protection wanted to be excluded. We continued the follow-up by evaluating the vaccine induced antibody responses in another study [11]. Other limitations include timing of serum sample collections that were not adjusted based

on positive COVID-19 PCR test result and moderate in-house EIA sensitivity with convalescent phase COVID-19 patient samples (96% for N based IgG EIA and 85% for S1 based IgG EIA) [10]. It is possible that some mild and asymptomatic SARS-CoV-2 infections were unidentified with serological assay due to generation of low levels of antibodies that decreased before follow up serum sample was collected or due to no seroconversion [12–14].

In our study cohort, 14 participants had antibodies only against SARS-CoV-2 N protein and one participant only against SARS-CoV-2 S1 protein. One of the explanations for being seropositive for SARS-CoV-2 N but not S specific antibodies is cross-reaction with seasonal human coronaviruses, since SARS-CoV-2 shares closely related nucleocapsid structure with other human coronaviruses [10,15]. Earlier studies have also suggested that anti-N antibodies are produced before anti-S antibodies in early-stage SARS-CoV-2 infection [16]. Since the anti-N antibody levels did not increase during follow-up and none of the anti-N seropositive participants turned anti-S seropositive later, the significance of only anti-N IgG antibodies remains unclear.

Conclusion

In a prospective surveillance study among HCWs with high occupational exposure to COVID-19, the prevalence of SARS-CoV-2 seropositivity remained low. In addition to high vaccine coverage, high standards of infection prevention practices and use of PPE seem important and effective in protecting HCWs from COVID-19 in a setting with low number of circulating virus. However, it remains unclear whether similar protective practices in the hospital would also be effective against more transmissible SARS-CoV-2 variants.

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Disclosure statement

No potential conflict of interest was reported by the author(s). The funding organisations had no role in the design, data analysis and publishing of the study.

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