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ACUTE SARS-CoV-2 INFECTION AND SEROPOSITIVITY AMONG HEALTHCARE WORKERS AND MEDICAL STUDENTS IN SUMMER 2020, HUNGARY

ANNAMÁRIA KOSZTIN[1], BÉLA MERKELY[1], ATTILA J. SZABÓ[2], BÉLA BLAHA[3], PÉTER VARGA[4], BARNA VÁSÁRHELYI[3], and ZOLTÁN VOKÓ[5]

Semmelweis University, Budapest, Hungary

[1] Heart and Vascular Center

[2] 1st Department of Pediatrics

[3] Department of Laboratory Medicine

[4] Clinical Centre

[5] Center for Health Technology Assessment

Abstract

Objectives: The aim was to compare the prevalence of acute infection and seropositivity of SARS-CoV-2 among healthcare workers (HCWs) and medical students. **Material and Methods:** A high-volume, single-center analysis was conducted in the period of July 1–August 1, 2020, at the Semmelweis University. Naso- and oropharyngeal samples were collected for polymerase chain reaction (PCR), and blood samples for anti-SARS-CoV-2 IgG. A questionnaire was also administered about the infection symptoms and the obtained results were assessed by profession and site of care delivery. **Results:** From the total cohort (N = 7948), 4478 (56%) and 3470 (44%) were health professionals and medical students, respectively. They were mainly female (67%), and the mean age of HCWs and students was 40 and 25 years, respectively. By profession, physicians (1.5%) and other HCWs (1.8%) showed a comparable SARS-CoV-2 exposure. International students had the highest (2.1%), whereas Hungarian students had the lowest (0.6%) prevalence of seropositivity. The highest prevalence was detected among the staff of COVID-19 wards (12.1%). By PCR, medical students showed the lowest occurrence of active infection with a prevalence of 0.17%, while physicians and other HCWs had a higher prevalence (1.46% and 1.71%, respectively). By site of care delivery, positive test results were the most frequent at COVID-19 wards (3.8%). **Conclusions:** Physicians and other HCWs showed comparable SARS-CoV-2 seropositivity prevalence, approximately twice as high as in the general population of Budapest. Hungarian students had lower prevalence of seropositivity than this reference. High prevalence among international students suggests that they had imported the infection. The very high prevalence of documented exposure among staff members at COVID-19 wards urges for improving the safety measures. Int J Occup Med Environ Health. 2022;35(2)

Key words:
polymerase chain reaction, medical students, seropositivity, COVID-19, SARS-CoV-2, healthcare workers

INTRODUCTION

Coronavirus disease 2019 (COVID-19) was declared by the World Health Organization (WHO) a public health emergency of international concern on January 30, 2020, and a pandemic on March 11 [1,2]. The disease is still spreading widely throughout the world.

Healthcare workers (HCWs) are at a high risk as the infection can be transmitted even by asymptomatic persons. Moreover, the main sources of infection with a high transmission rate are patients with severe symptoms [3], who are likely to be admitted to hospitals. Healthcare workers have a significant risk of exposure to SARS-CoV-2

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Corresponding author: Béla Merkely, Semmelweis University, Heart and Vascular Center, Városmajor 68 H-1122 Budapest, Hungary (e-mail: merkely.bela@kardio.sote.hu).

during work, which is confirmed by the reported high rates of COVID-19 infections among them [4]. However, the regional infection prevalence rates among HCWs vary widely [5–9], which might be explained by the number of infected and hospitalized patients, the accuracy of patient management, the use of personal protective equipment, and adherence to safety measures [6]. Those HCWs who cared for COVID-19 patients had higher rates of infection, but the risk increased to a lesser extent if they used personal protective equipment (3.5–4.8 higher rates vs. up to 6 times higher risk in the case of appropriate and inappropriate use) [6].

Although much data is available about SARS-CoV-2 infection among HCWs, including primarily among physicians and nurses, to the best of the authors' knowledge, similar data have not been published about medical students involved in practical education or in assisting patient care. Medical students also represent a relevant number of HCWs, at least at university hospitals. Moreover, based on their educational system, they more frequently change their locations between clinics or hospitals; nonetheless, they have less experience and routine with the use of personal protective equipment.

Therefore, the aim of the present study was to compare the prevalence of acute infection and seropositivity of HCWs and medical students at the largest Hungarian medical school with the results from the same geographic area (Budapest) of the representative, cross-sectional survey of the Hungarian general population (H-UNCOVER) [10].

MATERIAL AND METHODS

Study population

At the Semmelweis University, Budapest, Hungary, in the period of July 1–August 1, 2020, 7948 individuals were tested – 4478 (56%) HCWs, including physicians and other healthcare professionals, and 3470 (44%) medical students, of whom 1832 (53%) were international students and 1638 (47%) were Hungarian students. With regard to the country of origin, international students came from 70 different countries, most of them from Germany, South Korea, Norway, and Iran. Employees of those organizational and related service units (maintenance, security, reception, administration) involved in direct patient care were included. Since the first restrictive measures, employees of theoretical institutions of the university had been working in home office and used online systems; thus, they were excluded from the study. Among these students, those who were involved actively in voluntary healthcare or as part of their practical training were included.

The study protocol complies with the Declaration of Helsinki and it was approved by the Medical Research Council (IRB IV/4060-3/2020/EKU – H-UNCOVER) and the institutional review board and the local ethics committee (SE RKEB No. 210/2020).

Sites of care delivery

When the first confirmed COVID-19 cases were diagnosed in Hungary in March 2020, the Semmelweis University introduced an entrance system for each clinic, where single points were kept as an entrance separately for patients and for staff members. First, patients were triaged in the emergency unit, risk assessment was conducted by their current status, and then they were taken to green, gray, or red zones on designated routes. In the green zone, COVID-19 was not suspected. Suspicious cases were cared for in the grey zone. They were treated as COVID-19 positive until the results of PCR. At these intermediary wards, HCWs applied appropriate equipment for their self-protection. Confirmed COVID-19 patients were sent to the red zone. In this newly designed COVID-19 ward, different medical specialists and other HCWs provided medical services. A separated COVID-19 intensive care unit was available for those patients requiring intensive care located elsewhere than at the conventional ICU, and they were cared by designated staff.

Laboratory samples

Simultaneously with naso- and oropharyngeal samples, 5 ml of blood was also taken. In the subjects' sera, the presence of IgG antibodies against SARS-CoV-2 virus was tested with Abbott tests on the Architect i2000 immunoassay system.

Questionnaire

All participants filled in a short questionnaire when the samples were taken for the serological test. This covered their profession, site of care delivery, previous contact with a person quarantined or known to be infected with SARS-CoV2, and a history of shortness of breath or fever in the past 48 h.

Polymerase chain reaction

To detect or exclude the presence of the SARS-CoV-2 virus, naso- and oropharyngeal samples were collected in viral transport medium tubes and were transported to the laboratory at 2–8°C. After nucleic acid extraction real-time PCR was performed (HBRT-COVID-19, Chaozhou Hybribio Biochemistry Ltd., Chaozhou, Guangdong, China) within 24 h after sample collection. The test used detects the presence of 2 SARS-CoV2 viral genes and applies a human gene sequence as an internal quality control for sampling. The kit detects the amplification of 2 viral and 1 human gene; samples with no amplification were considered as invalid/inhibitory/inappropriate; those with the amplified human gene without the amplification of viral genes were considered as negative; those with the amplification of all tested genes were positive, and those with the amplification of just one viral gene with that of the human gene were considered as ambiguous.

Analysis of anti-SARS-CoV-2 IgG

Simultaneously with PCR sampling, blood samples were also obtained. Serological testing for SARS-CoV-2 specific IgG was performed with the Abbott SARS-CoV-2 IgG Reagent Kit (Cat No: 6R86-32 on the Architect i2000SR automated immunoassay system). The test is designed to detect immunoglobulin class G (IgG) antibodies to the nucleocapsid protein of SARS-CoV-2.

Statistical analysis

Some participants had more than one PCR or serological tests. In these cases, an individual was considered to have a positive test if any of the repeated tests had a positive result. The prevalence of seropositivity and PCR positivity was estimated by profession, and the participants were categorized as physicians, other HCWs, international medical students or Hungarian medical students enrolled in an international or Hungarian program. The authors also estimated prevalence by site of care delivery, categorized as a COVID-19 intensive care unit (COVID ICU), a COVID-19 general ward, a COVID-19 intermediary ward or other inpatient care.

Furthermore, the strength of the association between seropositivity and previous contact with a person quarantined or known to be infected with SARS-CoV2 was estimated, and so was the positive predictive value of the history of shortness of breath or fever during the epidemic, using the PCR and the serological test as a gold standard test to diagnose the presence or history of SARS-CoV-2 infection.

The authors compared their findings to the results of the national survey (H-UNCOVER) corresponding to the population of Budapest. The method employed in the H-UNCOVER study was previously reported [10]. Briefly, it was a representative survey of the Hungarian non-institutionalized population aged ≥14 years, estimating the prevalence of seropositivity and PCR positivity for SARS-CoV-2 in the first half of May 2020.

Confidence intervals (CI) of the prevalence of seropositivity and PCR positivity were estimated by normal approximation. Fisher's exact test was used to test the difference in the prevalence of seropositivity and PCR positivity by profession and site of care delivery because of the low

number of persons with a positive PCR test. The prevalence odds ratio of seropositivity comparing persons with and without the shortness of breath by profession was estimated by logistic regression using the statistical package STATA 16.0. As for the general population, the survey module of the package was used to provide designed based estimate (i.e., to take into account the sampling design of the survey). The analysis was not adjusted for other covariates.

RESULTS

Baseline clinical characteristics

From the total study population of 7948 persons who had undergone a serological test, 4478 (56%) were HCWs and 3470 (44%) were medical students. Of the students, 1832 (53%) were international students, while 682 (20%) Hungarian students were enrolled in the international program and 956 (27%) in the Hungarian training program (Table 1). The majority of HCWs (N = 2581, 88%) and also the majority of Hungarian students enrolled in the international program (N = 517, 76%) were female. Sex distribution in the other professional groups was more balanced. The mean age of HCWs was around 40 years, and the students' mean age was around 25 years in the 3 groups, respectively (Table 1).

Overall PCR positivity

Of the total study population, 4886 participants had undergone a PCR test, of which 45 (0.9%) results were positive. Four acute infections were found among the medical students, with a prevalence of 0.17% (95% CI: 0.003–0.3). Physicians and other HCWs had a higher prevalence – 1.46% (95% CI: 0.70–2.21), and 1.71% (95% CI: 1.07–2.34), respectively. The differences were statistically significant ($p < 0.001$). The prevalence of PCR positive test results was the highest among those who worked at COVID-19 wards (3.8%, 95% CI: 0–8.01). The prevalence was approx. 50% of this value among those who worked at intermediary wards (1.85%, 95% CI: 0.05–3.65), and <1% among HCWs at other wards (0.84%, 95% CI: 0.57–1.10). There were no positive findings among the COVID ICU workers tested.

Prevalence of seropositivity and symptoms

There was a statistically significant difference ($p = 0.04$) in the prevalence of seropositivity by profession. Physicians

Table 1. Characteristics of the population involved in the study on the prevalence of acute infection and seropositivity of SARS-CoV-2, conducted at the Semmelweis University, Budapest, Hungary, July 1–August 1, 2020

Profession	Participants (N = 6310)		Participants' age [years] (M±SD)
	total [n]	females [n (%)] (N = 4401)	
Physicians	1552	809 (52.1)	41.1±13.7
Other healthcare workers	2926	2581 (88.2)	43.7±11.6
Students			
international	1832	1011 (55.2)	24.7±3.8
Hungarian			
in the international program	682	517 (75.8)	25.7±7.5
in the Hungarian program	956	596 (62.3)	23.9±2.6

Table 2. Prevalence of seropositivity by profession among the participants (N = 6310) of the study conducted at the Semmelweis University, Budapest, Hungary, July 1–August 1, 2020

Profession	Seropositive participants [n]	Prevalence	
		%	95% CI
Physicians	24	1.5	0.9–2.2
Other healthcare workers	54	1.8	1.4–2.3
Students			
international	38	2.1	1.4–2.7
Hungarian			
in the international program	11	1.6	0.7–2.6
in the Hungarian program	6	0.6	0–1.1

(1.5%, 95% CI: 0.9–2.2) and other HCWs (1.8%, 95% CI: 1.4–2.3) showed a comparable SARS-CoV-2 exposure, <2% (Table 2). International students had the highest prevalence with 2.1% (95% CI: 1.4–2.7), whereas Hungarian students enrolled in the Hungarian program had the lowest with <1% (0.6%, 95% CI: 0–1.1).

Regarding the site of care delivery, the highest prevalence was at the COVID-19 wards (12.1%, 95% CI: 6.7–17.4), and a fifth of this value could be observed among those working at the intermediary wards (2.5%, 95% CI: 0.05–4.4), while it was 1.8% (95% CI: 0–4.3) among the COVID ICU workers. The lowest prevalence of seropositivity was found among HCWs working at other wards (1.4%, 95% CI: 0.1–1.7). The differences were statistically significant ($p < 0.001$).

Seropositivity prevalence was 6 times higher among those who reported a contact with someone infected by SARS-CoV-2 (6.8% vs. 1.1%, $p < 0.001$), and almost 10 times higher among those who contacted a quarantined person (10.5% vs. 1.1%, $p < 0.001$).

Seropositivity was detected in 17–25% of the participants reporting shortness of breath or fever since the beginning of March, except among Hungarian students enrolled in the Hungarian program (Table 3). This proportion did not exceed 2% in any of the study groups among those not reporting such symptoms. Shortness of breath increased the odds of infection by 3 times in the general population, but it was much more predictive among HCWs (12–41 times increased odds).

DISCUSSION

To the best of the authors' knowledge, this is the first analysis, which assessed the prevalence of SARS-CoV-2 virus infection and seropositivity in such a large population of healthcare providers (N = 7946), also involving medical students.

The results obtained by the authors showed that, except for medical students enrolled in the Hungarian program, seropositivity prevalence among HCWs was approximately twice as high as in May in the general population aged ≥14 years living in private households in Budapest (90/10000, 95% CI: 29–152) [10]. Among international students, the prevalence was more than twice as high as this value (the difference in the prevalence compared to the general population of Budapest was 1.2%, 95% CI: 0.3–2.1, $p < 0.01$). The low prevalence of PCR positivity indicates that very few infected HCWs were detected in the acute phase of the disease. By site of care delivery, the highest prevalence was found at the COVID-19 wards and not at the COVID ICU. The reason for this might be that only very few patients were admitted to the ICU, and

Table 3. Prevalence of seropositivity in the general population by profession and by reporting shortness of breath or fever since the start of the epidemic, in the study conducted at the Semmelweis University, Budapest, Hungary, July 1–August 1, 2020

Profession	Seropositive participants [n]		Seropositivity prevalence				OR (95% CI)*
	symptoms reported	symptoms not reported	symptoms reported		symptoms not reported		
			%	95% CI	%	95% CI	
General population	7	61	1.9	0.5–3.3	0.6	0.4–0.8	3.1 (1.4–6.8)
Physicians	12	12	25.0	12.8–37.2	0.8	0.3–1.2	41.4 (17.4–98.5)
Other healthcare workers	14	40	16.9	8.8–24.9	1.4	1.0–1.8	14.2 (7.4–27.3)
Students							
international	1	37	20.0	0–55.1	2.0	1.4–2.7	12.1 (1.3–110.8)
Hungarian							
in the international program	1	10	16.7	0–46.5	1.5	0.6–2.4	13.3 (1.4–124.6)
in the Hungarian program	0	6	0		0.6	0.1–1.1	–

* Odds of seropositivity among people reporting symptoms compared to those who did not report them.

although there was no difference detected by site of care delivery and profession in the acceptance of personal protective equipment, the staff of the ICU was better trained and experienced in using safety measures similar to those which were applied because of the epidemic.

Previous reports about the prevalence of infection among HCWs ranged 3.8–29% [4]. The infection among HCWs depends on several factors including the infection rate in society, the use of safety measures, patient pathways and the management of confirmed, symptomatic patients, education of HCWs, and their adherence to safety protocols. Although safety measures do not eliminate completely the risk of infection, the appropriate use of personal protective equipment can considerably reduce it [6].

In a recent study, the prevalence of acute SARS-CoV-2 infection was compared in 546 HCWs serving in a large U.S. university and 2 affiliated university hospitals, and in 283 non-HCWs (faculty, staff, trainees, or students without patient contact). The prevalence of the infection was assessed as 7.3% among HCWs and 0.4% among non-HCWs. The infection rate was reported to be the highest among nurses (11.1%), while ICU workers showed the lowest prevalence (2.1%) compared to other units (4.9–9.7%), consistently with the authors' findings [9]. Another recent ahead-of-print report stated that more than half of the infected HCWs were physicians, mostly general practitioners and primary care physicians. Anesthesiologists, emergency medicine and critical care physicians only accounted for 7.4% of the cases, which also proves the relevance of personal equipment and the importance of practice [8]. In this study, there was no difference between physicians or other HCWs, but the site of care delivery. The high prevalence of infection among COVID-19 ward workers in this study highlights the need for improving the training and the infection control.

The higher prevalence of seropositivity among individuals having experienced shortness of breath or fever among HCWs compared to those who did not experience such symptoms shows that these symptoms can be used efficiently to prescreen HCWs otherwise not selected for testing. The odds of seropositivity were 40 times higher among symptomatic physicians than among those who did not experience shortness of breath or fever.

While medical students participate in the everyday clinical practice, data are scarce about the prevalence of acute SARS-CoV-2 infection and seropositivity among them. Based on the educational system, they rotate their locations more frequently between the institutions and they also have less experience with treating such infected patients. So far there have been no data published on the extent to which this population is affected by the epidemic. This analysis showed that the highest risk was among the international students. This was likely because of the higher prevalence of infection in their country of origin, as most of them returned back to Hungary after the epidemic started, and the prevalence of PCR positivity was low among them during the study phase. The difference in the prevalence among the Hungarian students enrolled in the international and Hungarian programs indicates that most sources among them were imported.

Notably, this study has some limitations. First, HCWs and medical students were selected for testing for infection control reasons. Therefore, they might not fully represent all HCWs and students of the university. Second, the elapsed time between the representative national survey (May 1–16) and the tests performed in this study (July 1–August 1, 2020). Nevertheless, the epidemic showed a stable period at that time with a very low number of reported cases.

CONCLUSIONS

In this high-volume single-center retrospective analysis, physicians and other HCWs showed comparable SARS-CoV-2 seropositivity prevalence, which was approximately twice as high as in the general population of Budapest. Except for the HCWs working at COVID-19 wards, the prevalence of seropositivity was lower among HCWs in this study than the reference data reported in literature. Medical students were well protected from the infection as Hungarian students enrolled in the Hungarian program had lower seropositivity than in the national survey in Budapest. International students had the highest prevalence, and they were the likely source of most infection cases among the Hungarian students enrolled in the international program. The very high prevalence of infection among employees at COVID-19 wards urges for improving the safety measures there.

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