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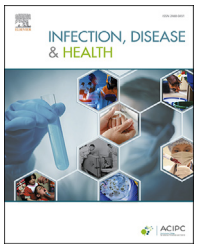

Research paper

SARS-CoV-2 seroprevalence in healthcare workers and risk factors

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KEYWORDS
SARS-CoV-2;
Healthcare worker;
Seroprevalence;
Smoking

Abstract *Background:* Exposure of healthcare workers (HCW) to SARS-CoV-2 is a public health concern. Not only are HCWs particularly exposed to SARS-CoV-2, but their contamination can also weaken the healthcare system.
Methods: We analyzed exposure of French University Hospital HCWs to SARS-CoV-2 through history of positive RT-PCR test and SARS-CoV-2 seroprevalence. Potential risk factors, such as age, BMI, having children or not, working in a COVID-19 unit, or smoking were explored.
Results: From May to June 2020, among the 8960 employees of the University Hospital of Nancy, a serological test was performed in 4696 HCWs. The average (SD) age was 40.4 (11.4) years, and the sample included 3926 women (83.6%). Of the 4696 HCWs, 1050 were smokers (22.4%). Among them, 2231 HCWs had a history of COVID-19 symptoms and/or flu-like syndrome (47.5%) and 238 were seropositive (5.1%). Neither gender, sex, BMI, nor having children were associated with a history of positive RT-PCR test or seropositive status. Previous work in a COVID-19 unit was associated with a history of positive RT-PCR test ($p = 0.045$), but not with seroprevalence ($p = 0.215$). As expected, history of COVID-19 clinical manifestations was more frequent in HCWs with positive serology than in HCWs with negative serology (adjusted OR = 1.9, 95%CI [1.4—2.5], $p < 0.001$). Less expected, smoking was associated with a reduced risk of seropositivity among HCWs (adjusted OR = 0.6, 95%CI [0.4—0.9], $p = 0.019$).

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Conclusion: HCW are patently exposed to SARS-CoV-2. Care to COVID-19 patients was not associated with a higher SARS-CoV-2 seroprevalence. Smoking appears here associated to a lower seroprevalence.

Highlights

- 47.5% of HCWs 47.5% had a history of COVID-19 symptoms.
- 5.1% of HCW were seropositive.
- Neither gender, sex, BMI, nor having children were associated with seropositive status.
- Working in a COVID-19 unit was associated with positive RT-PCR test.
- Smoking was associated with a lower seroprevalence among HCWs.

Introduction

Healthcare workers (HCW) play a crucial role in the first and current response to the SARS-CoV-2 pandemic. They have been identified as a group at high risk of infection due to frequent and close contacts with COVID-19 patients (World Health Organization, 2020). The protection of HCWs is critical for pandemic control, both at the individual level for the continuity of care and at the collective level to avoid transmission to their professional and personal contacts [1].

The Northeast of France was particularly impacted by the first epidemic wave. The EpiCoV survey conducted in May 2020 revealed that seroprevalence was highest in Paris (9%), and the Haut-Rhin department (10.8%), located in the Northeast of France, was the epicenter of the start of the epidemic in France. Seroprevalence in the whole Northeast of France was from 6.7% in May 2020 [2].

The aim of the present study was (i) to describe the seroprevalence of SARS-CoV-2 in HCWs at Nancy University Hospital, located in the Northeast of France; (ii) to determine whether sex, age, BMI, having children, working in a COVID-19 unit, or smoking can be considered as risk factors for SARS-CoV-2 infection.

Methods

Study design and participants

This study was a single-centre seroprevalence survey of HCW from a single time point. On May 2020, the French Health Minister offered SARS-CoV-2 serological screening to all HCWs. At Nancy University Hospital, HCWs who underwent blood sampling and serological analyses were asked to fill in a form to collect epidemiological and clinical data. All HCWs who completed this form were included in the study (Fig. 1). HCWs included medical staff, nursing staff, and maintenance staff.

Collected data included date of birth, gender, height, weight, smoking status (smoker/non-smoker), working in a COVID unit or not, having children or not (and age range), having been screened for SARS-CoV-2 (RT-PCR) or not (dates of screening and results when appropriate), flu-like syndrome (fever, body aches, headache), dry cough, gastrointestinal symptoms, loss of taste/smell, influenza vaccination (and if so, date).

Serological assay

Blood samples were collected in a dry SST tube with serum-PET separator. Due to the high number of samples collected over a short period of time, SARS-CoV-2 serologies were performed using various techniques.

The BYOSYNEX® COVID-19 BSS technique is a flow lateral immunoassay for qualitative detection of anti-SARS-CoV-2 IgM and IgG. The target protein is the Receptor Binding Domain (RBD) of the Spike S protein. According to the manufacturer, the sensitivity for IgG is 100% and the specificity is 99.5%, and the sensitivity for IgM is 91.8% and the specificity is 99.2%.

The MagLumi COVID-19® test is an automated method based on chemiluminescence immunoassay. This test allows a semi-quantitative detection of anti-SARS-CoV-2 IgM and IgG directed against the receptor binding domain of protein S and the nucleocapsid (N) proteins. According to the manufacturer, the threshold of positivity is 1 AU/mL for IgM and IgG. For IgG, the sensitivity is 100% and the specificity is 99.1% 15 days after onset of the first post-infection symptoms. For IgM, the sensitivity is 77.46% and the specificity is 99.6% 15 days after onset of the first post-infection symptoms.

Euroimmun® SARS-CoV-2 ELISA is a test for quantitative detection of anti- SARS-CoV-2 IgA and IgG by Enzyme-Linked Immunosorbent Assay (ELISA). The Euroimmun® SARS-CoV-2 ELISA uses a recombinant S1 domain of protein S as target. Results are expressed as a ratio; a final ratio greater than 1.2 indicates positive serology. For IgG, the sensitivity is 90% and the specificity is 100% 10 days after onset of the first post-infection symptoms. For IgA, the sensitivity is 100% and the specificity is 92.5% 10 days after the first post-infection symptoms.

Ambiguous results were confirmed by another method, according to a unique flow chart: Positive IgM detected by BYOSYNEX® or MagLumi® methods without IgG detection were confirmed or invalidated by complementary

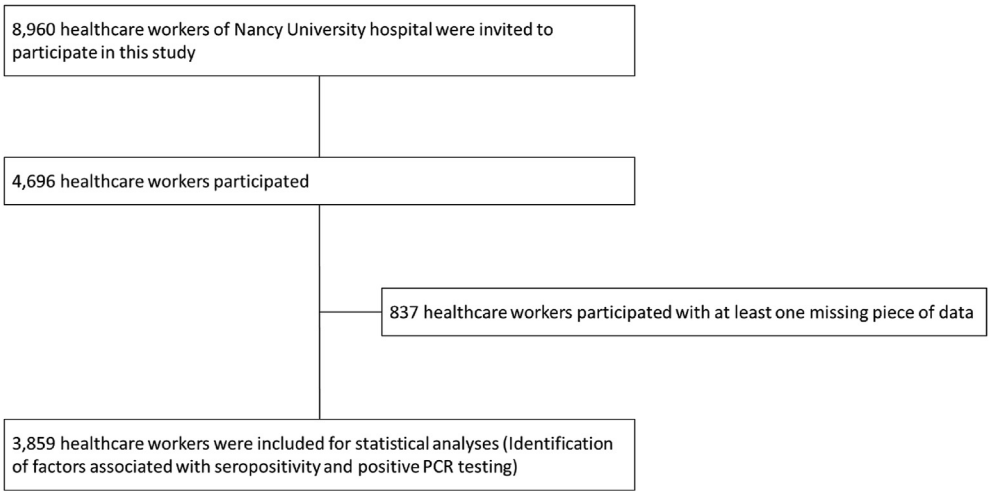

Figure 1 Flow chart of the COVIDOSOIN study.

techniques. Doubtful IgA detected by the EUROIMMUN® method (ratio $\geq$0.8 to $<$1.1) were confirmed or invalidated by MagLumi® technique.

Statistical analysis

A stratified description of HCW characteristics was performed according to serological status (positive vs. negative serology) and according to history of RT-PCR test result (positive vs. negative RT-PCR test), using frequencies and percentages for qualitative variables and mean and standard deviation for quantitative variables. HCW characteristics were then compared between groups, using Student's t-test/ANOVA or Wilcoxon/Kruskal–Wallis tests for quantitative variables, and Chi-square or Fisher's exact tests for qualitative variables according to the condition of use.

To identify factors associated with seropositivity or with history of RT-PCR positivity (i.e., at least one positive RT-PCR test among the RT-PCR tests performed), a bivariate logistic regression model was implemented for each HCW characteristic, entering seropositivity (or RT-PCR positivity) as the dependent variable, and HCW characteristic as the independent variable. A stepwise procedure was implemented to identify factors associated with seropositivity, with a significance level for entry (sle) set at 0.2 and a significance level for stay (sls) at 0.05. Results were reported as odd ratios (OR) and 95% confidence intervals (95% CI). *P* values were two-sided. Significance level was set at 0.05. Statistical analyses were performed using SAS 9.4 (SAS Institute, Inc., Cary, NC).

Results

Description of the cohort

From May 25, 2020 to June 29, 2020, 4696 HCWs out of the 8960 employees of University Hospital of Nancy underwent a serological test. A total of 3926 women (83.6%) and 770 men (16.4%) were included; the average (SD) age was 40.4 (11.4) years. All participants completed the COVIDOSOIN form.

Among the 2231 HCW with a history of COVID-19-associated clinical signs (47.5%), flue-like syndrome was predominant (30.3% of HCW).

Overall, 79.2% of included HCWs had worked in a COVID-19 unit. A total of 238 study participants were seropositive (5.1%) and 131 participants had a history of at least one positive RT-PCR test (2.8%).

In terms of epidemiological characteristics, 1050 participants were smokers (22.4%); 21.8% were overweight and 10.7% were obese; 64.2% of HCWs interviewed had one or more children (Table 1).

Epidemiological and clinical factors associated with a history of positive RT-PCR test

When comparing HCWs with or without any history of positive RT-PCR test, no difference was observed in terms of age, sex, BMI, smoking, and having children (S1). HCWs with a history of positive RT-PCR test were more likely to have a history of COVID-19-associated clinical signs symptoms compared with HCWs without any history of positive RT-PCR test, whether for all syndrome and symptoms combined (98.5% vs. 46.6%, $p < 0.001$) or each taken one by one (S2). HCWs with a history of positive RT-PCR test were more likely to have worked in a COVID-19 unit than those with no history of positive RT-PCR (86.3% vs. 79.0%, $p = 0.045$).

Epidemiological and clinical factors associated with positive SARS-cov-2 serology

HCWs with positive serology were more likely to have a history of positive RT-PCR test than HCWs with negative serology (28.2% versus 1.5%, $p < 0.001$). History of COVID-19-associated clinical signs was also more frequent in HCWs with positive serology than in HCWs with negative serology, whether for all clinical signs combined (63.9% versus 47.2%, $p < 0.001$) or for each taken separately (S2). Participants who had worked in a COVID-19 unit were equally likely to be seropositive than those who did not work in a COVID-19 unit ($p = 0.215$).

Table 1 Global description of the cohort.

	all	
	N = 4696	
Age in 2020 (years)		
N	4696	
Mean ± SD [95%CI]	40.4 ± 11.4 [40.1; 40.7]	
Median (Q1 - Q3)	40.0 (30.0—50.0)	
Min - Max	18.0—71.0	
Gender		
Male	770	(16.4%)
Female	3926	(83.6%)
BMI		
NS	296	(6.3%)
Underweight	159	(3.4%)
Normal weight	2714	(57.8%)
Overweight	1023	(21.8%)
Obesity	504	(10.7%)
Smoking		
NS	197	(4.2%)
Yes	1050	(22.4%)
No	3449	(73.4%)
Children (all ages)		
NS	19	(0.4%)
Yes	3013	(64.2%)
No	1664	(35.4%)
Children under 2 years old		
NS	19	(0.4%)
Yes	358	(7.6%)
No	4319	(92.0%)
Children between 2 and < 5 years old		
NS	19	(0.4%)
Yes	539	(11.5%)
No	4138	(88.1%)
Children between 5 and < 10 years old		
NS	19	(0.4%)
Yes	776	(16.5%)
No	3901	(83.1%)
Children between 10 and < 15 years old		
NS	19	(0.4%)
Yes	917	(19.5%)
No	3760	(80.1%)
Children aged 15 years and older		
NS	19	(0.4%)
Yes	616	(13.1%)
No	4061	(86.5%)
Seropositivity		
Positive	238	(5.1%)
Negative	4458	(94.9%)
Working in a COVID-19 unit		
Yes	3718	(79.2%)
No	978	(20.8%)
RT-PCR Screening		
NS	45	(1.0%)
Yes	629	(13.4%)
No	4022	(85.6%)
At least one positive RT-PCR test		
NS	45	(1.0%)
Yes	131	(2.8%)
No	4520	(96.3%)
COVID-19 clinical manifestations (all)[a]		
NS	55	(1.2%)
Yes	2231	(47.5%)
No	2410	(51.3%)
Influenza-like syndrome		
NS	187	(4.0%)
Yes	1421	(30.3%)
No	3088	(65.8%)
Dry cough		
NS	267	(5.7%)
Yes	1155	(24.6%)
No	3274	(69.7%)
Gastrointestinal symptoms		
NS	316	(6.7%)
Yes	967	(20.6%)
No	3413	(72.7%)
Loss of taste/smell		
NS	428	(9.1%)
Yes	258	(5.5%)
No	4010	(85.4%)
Flu vaccine		
NS	4	(0.1%)
Yes	1871	(39.8%)
No	2821	(60.1%)
Flu diagnosis		
Yes	86	(1.8%)
No	4610	(98.2%)

NS: Not specified.
[a] COVID-19 clinical manifestations: flu-like syndrome, dry cough, gastrointestinal symptoms, loss of taste/smell.

Using a multivariate analysis, age, sex, BMI, and having children (regardless of their age) were not risk factors for SARS-COV-2 seropositivity, neither having worked in a COVID-19 unit (Table 2). Loss of smell or taste was a risk factor for SARS-CoV-2 seropositivity (adjusted OR = 4.2, 95%CI [2.6—6.7], $p < 0.001$).

Finally, smoking was associated with a reduced risk of seropositivity (adjusted OR = 0.6, 95%CI [0.4—0.9], $p = 0.019$) (Table 2).

Discussion

In the present study, we evaluated the seroprevalence of SARS-CoV-2 in 4696 HCWs at Nancy University Hospital, Northeast France. Data concerning sex, age, BMI, having children, working in a COVID-19 unit, or smoking were collected as well as history of positive SARS-CoV-2 RT-PCR and clinical signs associated with COVID-19, meaning flu-like syndrome, dry cough, gastrointestinal symptoms, loss of taste/smell. The major finding of this study is the confirmed association between COVID-19 seropositive status and a history of COVID-19 associated clinical signs (all types). No effect of sex, age, BMI, and having children was

Table 2 Factors associated with positive seropositivity status.

	N	Seropositivity		Bivariate regression					Multivariate regression[b]				p
		n	%	Odds ratio	95%CI[a]			p	Odds ratio	95%CI[a]			
					Inf[a]		Sup[a]			Inf[a]		Sup[a]	
Age in 2020								0.497					
<30 years	923	42	4.6	1									
30–39 years	1068	48	4.5	1.0	0.6	–	1.5						
40–49 years	901	53	5.9	1.3	0.9	–	2.0						
≥50 years	967	48	5.0	1.1	0.7	–	1.7						
Sex								0.989					
Male	648	32	4.9	1.0	0.7	–	1.5						
Female	3211	159	5.0	1									
BMI								0.029					
Normal weight	2392	113	4.7	1									
Underweight	143	2	1.4	0.3	0.1	–	1.2						
Overweight	884	56	6.3	1.4	1.0	–	1.9						
Obesity	440	20	4.5	1.0	0.6	–	1.6						
Smoking								0.002					0.019
Yes	884	27	3.1	0.5	0.4	–	0.8		0.6	0.4	–	0.9	
No	2975	164	5.5	1					1				
Children (all ages)								0.456					
Yes	2442	116	4.8	0.9	0.7	–	1.2						
No	1417	75	5.3	1									
Children under 2 years old								0.416					
Yes	300	12	4?0	0.8	0.4	–	1.4						
No	3559	179	5.0	1									
Children between 2 and < 5 years old								0.548					
Yes	456	20	4.4	0.9	0.5	–	1.4						
No	3403	171	5.0	1									
Children between 5 and < 10 years old								0.785					
Yes	639	33	5.2	1.1	0.7	–	1.6						
No	3220	158	4.9	1									
Children between 10 and < 15 years old								0.449					
Yes	747	33	4.4	0.9	0.6	–	1.3						
No	3112	158	5.1	1									
Children aged 15 years and older								0.697					
Yes	500	23	4.6	0.9	0.6	–	1.4						
No	3359	168	5.0	1									
Working in a COVID-19 unit								0.223					
Yes	3104	160	5.2	1.3	0.9	–	1.9						
No	755	31	4.1	1									
At least one positive RT-PCR test								<0.001					<0.001
Yes	94	45	47.9	22.8	14.7	–	35.2		9.9	5.8	–	16.8	
No	3765	146	3.9	1					1				
COVID-19 clinical manifestations [c]								<0.001					
Yes	1660	110	6.6	1.9	1.4	–	2.5						
No	2199	81	3.7	1									
Flu-like syndrome								<0.001					
Yes	1051	91	8.7	2.6	1.9	–	3.4						
No	2808	100	3.6	1									
Dry cough								<0.001					
Yes	881	74	8.4	2.2	1.7	–	3.0						
No	2978	117	3.9	1									
Gastrointestinal symptoms								0.007					
Yes	746	52	7.0	1.6	1.2	–	2.2						
No	3113	139	4.5	1									
Loss of taste/smell								<0.001					<0.001
Yes	183	52	28.4	10.1	7.0	–	14.5		4.2	2.6	–	6.7	
No	3676	139	3.8	1					1				

(*continued on next page*)

Table 2 (*continued*)

	N	Seropositivity		Bivariate regression					Multivariate regression[b]			*p*
		n	%	Odds ratio	95%CI[a]			*p*	Odds ratio	95%CI[a]		
					Inf[a]		Sup[a]			Inf[a]	Sup[a]	
Flu vaccine								0.02				
Yes	1525	91	6.0	1.4	1.1	—	1.9					
No	2334	100	4.3	1								

NS: Not specified.
[a] CI: Confidence interval - Lower bound - Upper bound.
[b] Only factors with a significant association at the 0.2 threshold in the bivariate model were included.
[c] Variables that are not candidates for the multivariate model.

observed on COVID-19 seropositive status. Unexpectedly, smoking was found to be associated to a lower seroprevalence.

We compared our results to that of other studies that evaluated HCW SARS-CoV-2 seroprevalence, keeping in mind that results may be impacted by time-point and window for sampling. On the one hand, the seroprevalence of SARS-CoV-2 in HCW reached 7% In a study including 230,398 HCWs from 24 countries located all over the world (Europe, USA, China, Singapore, Mexico, India, South Korea), and 11% in a French national study [2], higher than in our hospital. On the other hand, lower seroprevalences were observed in Danish HCWs (4.04%) [3] and in a children's hospital in Southern Italy (1.3%) [4]. In the latter Italian study, the low seroprevalence was attributed to the strict application of preventive measures, with a strongly enforced policy of personal protective equipment (PPE) [4].

SARS-CoV-2 seroprevalence of Nancy University Hospital HCW (5.1%) was lower than that in the Whole Northeast of France (6.7%) but higher to that of the Nancy Town (2.1%) metropolis [5]. Yet, seroprevalence was not associated with working in a COVID-19 unit. We can therefore assume that the protection protocols were well applied and made hypothesis that HCWs may also have been contaminated outside the hospital. As an example, other studies demonstrated that community and public transportations were risk factors for seroconversion in HCWs [6], as well as social contact [4].

Locally, another study evaluated the seroprevalence in laboratory staff of the same university hospital. This one was almost equal to that of local general population [5,7] and lower compared to HCWs. When handling samples, laboratory technicians are better protected than HCWs, in particular through the use of microbiological safety stations in addition to PPE [7].

Our study revealed a negative association between smoking and the risk of being infected by SARS-CoV-2, analyzed by serology. This effect was not reported with RT-PCR analyses. But RT-PCR was not systematically realized, and this can lead to bias, if RT-PCR was realized more frequently in symptomatic and/or contact HCWs. The effect of smoking on SARS-CoV-2 infection is still debated. Lower SARS-CoV-2 infection rates among smokers has been previously described (Table 3). Notably, in a Chinese study of 1099 patients with COVID-19 performed until January 29, 2020, the proportion of smokers was 12.6% which is lower than the proportion of smokers in China (28%) [8]. Miyara et al. also reported that daily smokers are less likely to develop symptomatic or severe SARS-CoV-2 infection compared with the general population. This risk in smokers versus non-smokers is five and four times lower in outpatients and inpatients, respectively [9]. The Italian observational study MUSTANG-OCCUPATION-COVID 19 found that among the current smokers, 19.6% were seropositive whereas 9.2% had not antibodies against SARS-CoV-2 [10]. Contradictory results were observed in other countries [11,12].

Concerning the durability of humoral protection, a study of a sample of Italian healthcare workers showed that BioNTech-Pfizer COVID-19 vaccine-induced antibody titers declined more rapidly in current smokers than in non-smokers (211.80 AU/mL vs. 487.50 AU/mL at 60 days after the end of the vaccination cycle). Current smokers showed significantly lower antibody titers or a more rapid decline in vaccine-induced IgG compared with nonsmokers. This shows that active smoking has a negative impact on the humoral response to BioNTech-Pfizer COVID-19 vaccines. It would be interesting to know if this negative impact also occurs in case of natural infection with Sars-CoV-2 [13].

In the urban area of the University Hospital of Nancy, another study (MAGIC) was conducted to better define the association of SARS-CoV-2 seroprevalence and tobacco consumption. The study compared three groups, i.e. smokers (> 5 cigarettes/day), people in the process of quitting smoking using nicotine replacements, and non-smokers. The study included HCWs as well as people from the general population, aged over 18 years. Small numbers in each group did not allow for observing significant differences, but the same trend was observed. People consuming tobacco and people consuming nicotine replacements tended to have a smaller SARS-CoV-2 seroprevalence (n = 4/62 seropositive in smoker or nicotine replacement groups and 16/113 in non-smoker groups, respectively, $p = 0.16$). This suggests that nicotine may have an effect on the susceptibility to SARS-CoV-2 infection.

The association between SARS-CoV-2 infection and smoking is still debated, but so is the mechanism of action of nicotine and tobacco. On the one hand, smoking was associated with the down regulation of ACE2 (the SARS-CoV-2 cell receptor) and can thus reduce entry of viral particles into cells [14], and on the other hand ACE2 gene expression has been described as significantly increased in cells exposed to high nicotine concentration [15]. We may want to keep in mind that smoking has a structural impact

Table 3 COVID-19 risk factors associated with smoking: literature data.

Reference	Study population	Population size	Results	Conclusion
Rentsch et al., 2020 [17]	Patients hospitalized and/or in intensive care units	3789	OR = 0.45, 95%CI [0.35—0.57]	Current smoking was associated with decreased likelihood of COVID-19
Guan et al., 2020 [8]	Patients hospitalized and/or in intensive care units	661	OR = 0.20, 95%CI [0.08—0.51] Adjustment for age: OR = 0.23, 95%CI [0.09—0.59] Adjustment for occupation: OR = 0.27, 95%CI [0.10—0.71]	Smoking was found to be associated with a lower risk of infection, and this association remained significant after adjustment for age or occupation
De Lusignan et al., 2020 [18]	Outpatients	3802	Adjusted OR = 0.49; 95%CI [0.34—0.71]	Active smoking was associated with decreased odds of positive test result
Miyara et al., 2022 [9]	Outpatients	479	OR = 0.24, 95% CI [0.12—0.48]	The rate of active daily smoking was significantly lower in COVID-19 patients than in the general 2019 French population after standardization by age and gender
	Hospitalized patients	479	OR = 0.24, 95%CI [0.14—0.40]	
Jackson et al., 2021 [12]	Outpatients	53,002	Adjusted OR = 1.79, 95%CI [1.22—2.62]	Current smoking was independently associated with self-reported confirmed COVID-19 infection
Mostafa et al., 2021 [11]	Healthcare workers	4040	Former smokers: adjusted OR = 0.45, 95%CI [0.11—1.89] (p = 0.273) Current smokers: adjusted OR = 0.65, 95%CI [0.38—1.09] (p = 0.101)	Former or recent smoking was not associated with positive SARS-CoV-2 test results in HCWs

on the respiratory tract and alters the immune system, which generally makes smokers more susceptible to viral and bacterial infections of the lungs [16]. Therefore, it obviously cannot be proposed as a prevention tool.

The present study has limitations such as self-declaration of epidemiological and clinical data. Moreover, due to the large flow of blood sampling performed over a short period of time, various methods had to be used for anti-SARS-CoV-2 antibodies detection. The three methods used all included anti-Spike antibodies detection. They were all validated according to the same local certification criteria and using the same samples. Finally, the same algorithm was applied irrespective of the method used, with the aim to eliminate false positive reaction when only IgM or IgA were positive. Finally, due to the retrospective design of the study we cannot assess the chronological sequence from symptom onset to RT-PCR testing nor when people worked in a COVID-19 unit.

The strength of the study is the short collection time for all 4696 samples, which enabled a precise evaluation of University Hospital HCWs serological status. The study was performed at an optimal time, i.e., two months after the first epidemic wave in Northeast France. Indeed, the sensitivity of anti-SARS-CoV-2 antibodies detection methods is optimal more than 14 days after the infection, and post-infectious antibodies were described to be detectable for 6—7 months.

The profile of the epidemic is now completely different, since variants with modulated infectiveness emerged, and HCWs can now benefit from vaccination. All studies analyzing the beginning of the epidemic, including the present one, are precious to improve knowledge on HCW

exposure to recently emerging viruses and could no longer be performed as SARS-CoV-2 seropositive status is currently indifferently associated with past infection or vaccination.

Ethical consideration

Ethical approval was not provided for this study on human participants because this was a non-interventional study. Biological materials were obtained via standard care (no supplemental sampling) and data were analyzed anonymously.

Authorship statement

Stéphanie Weber: Investigation, Data Curation, Writing - Original Draft, Visualization. **Alice Didelot**: Investigation, Data Curation, Writing - Original Draft, Visualization. **Nelly Agrinier**: Methodology, Validation, Formal analysis, Writing - Review & Editing. **Laurent Peyrin Biroulet**: Conceptualization, Writing - Review & Editing. **Evelyne Schvoerer**: Conceptualization, Writing - Review & Editing. **Christian Rabaud**: Conceptualization, Writing - Review & Editing, Supervision, Project administration. **Hélène Jeulin**: Conceptualization, Methodology, Resources, Writing - Review & Editing, Project administration.

Conflict of interest

No conflict of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.idh.2022.05.002.

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