La Medicina del Lavoro

Original article

Med Lav 2023; 114 (3): e2023022
DOI: 10.23749/mdl.v114i2.14422

Factors Associated with SARS-CoV-2 Infection before Vaccination among European Health Care Workers

Ihab Mansour[1], Alessandro Godono[1*], Emanuele Sansone[2], Giovanni Visci[3], Gianluca Spiteri[4], Maria Grazia Lourdes Monaco[4], Dana Mates[5], Agripina Rascu[6], Xavier Duval[7], Enrico Pira[1], Catalina Ciocan[1], Francesco Violante[3,8], Vittorio Lodi[8], Giuseppe De Palma[2], Emma Sala[9], Marco Dell'Omo[10], Corrado Negro[11], Loretta Casolari[12], Mahsa Abedini[3], Giorgia Ditano[3], Shuffield Asafo[3], Paolo Boffetta[3,13], on behalf of the Orchestra WP5 Working Group[1]

[1]Department of Public Health and Pediatric Sciences, University of Turin, Turin, Italy
[2]Unit of Occupational Health and Industrial Hygiene, Department of Medical and Surgical Specialties, Radiological Sciences and Public Health, University of Brescia, Brescia, Italy
[3]Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy
[4]Clinical Unit of Occupational Medicine, University Hospital of Verona, Verona, Italy
[5]National Institute of Public Health, Bucharest, Romania
[6]University of Medicine and Pharmacy "Carola Davila", Bucharest, Romania
[7]Inserm CIC 1425, IAME, Bichat Claude Bernard hospital, Paris, France
[8]Occupational Health Unit, Sant'Orsola University Hospital, Bologna, Italy
[9]ASST Spedali Civili di Brescia, Italy
[10]Section of Occupational Medicine, Respiratory Diseases and Toxicology, University of Perugia, Perugia, Italy
[11]Unit of Occupational Medicine, University of Trieste, Trieste, Italy
[12]Health Surveillance Service, University Hospital of Modena, Modena, Italy
[13]Stony Brook Cancer Center, Stony Brook University, Stony Brook, NY, US

Keywords: COVID-19; Determinants; HCWs; Meta-analyses; Multicentric; Mask; FFP2

Abstract

Background: *Health care workers (HCWs) were on the frontline of the current pandemic. We aimed at identifying determinants of SARS-CoV-2 infection and the effectiveness of personal protection equipment (PPE) worn by HCWs before vaccination.* **Methods:** *We abstracted data on SARS-CoV-2 infection based on positive PCR results and sociodemographic characteristics of 38,793 HCWs from public hospitals and public health authorities from 10 European centers. We fitted cohort-specific multivariate logistic regression models to identify determinants of infection and combined the results using random-effects meta-analyses.* **Results:** *The overall prevalence of infection before vaccination among HCWs was 9.58%. Infection was associated with the presence of selected symptoms; no association was found between sociodemographic factors and increased risk of infection. The use of PPE and particularly FFP2/FFP3 masks had a different protective effect during the first and second waves of the COVID pandemic.* **Conclusions:** *The study provides evidence that mask use was the most effective PPE in preventing SARS-CoV-2 infection among HCWs.*

Received 09.03.2023 - Accepted 12.04.2023

[1]**WP5 Working Group:** Stefano Porru, Giuseppe Verlato, Angela Carta, Marina Ruxandra Otelea, Felicia Steliana Popescu, Lavinia Calugareanu, Madalina Ipate, Tubiana Sarah, Burdet Charles, Manchon Pauline, Giuliano Curoso, Giulia Collatuzzo, Carlo Bonfanti, Massimo Lombardo, Elisa Albini, Giacomo Muzi, Nicola Murgia, Marcella Mauro, Francesca Rui, Fabriziomaria Gobba, Alberto Modenese.

*Corresponding Author: Alessandro Godono, Department of Public Health and Pediatric Sciences, University of Turin, Turin, Italy; E-mail: alessandro.godono@unito.it.

1. Introduction

During the COVID-19 pandemic, healthcare workers (HCWs) were employed on the frontline to guarantee patient care, having higher exposure to SARS-CoV-2 infection than the general population [1]. Following the WHO recommendations, an intense activity of contact tracing and management of SARS-CoV-2-positive HCWs was established in many health facilities since the very beginning of the pandemic. These protocols have achieved remarkable results in identifying the determinants of infections and, consequently, updating risk assessment evaluation and establishing effective prevention measures [2].

During the early stages of the pandemic, several studies highlighted the importance of the correct use of personal protection equipment (PPE), its efficacy in terms of protection [3], both for surgical masks and FFP 2/3 [4], and the high tolerance profile [5]. As a consequence, European governments put specific measures to improve supply chains and provisions of PPE during the SARS-CoV-2 pandemic [6, 7]. Nevertheless, the incorrect use of PPEs documented during the SARS outbreak in 2005 [8] has often been an issue of concern in the current pandemic. Even among experienced HCWs, the importance of the correct use of PPEs has generally been underestimated: the right donning and doffing procedures are not routinely followed [9]. Thus, the protective effect of PPE may vary widely. In such a scenario, assessing the maximum theoretical efficacy of different PPEs can be difficult, while measuring their effectiveness in the field is of great clinical and public health importance.

Despite the COVID-19 vaccination campaign, which started in Europe in December 2020, proved to be very effective in preventing severe and symptomatic SARS-CoV-2 cases [10, 11], breakthrough infections (BIs) after vaccination occurred all over the world, both in the general population and among HCWs [12]. Initially related to the waning of the humoral response [13-16] and to the appearance of new virus variants [17], they can also occur after booster dose administration [14]. Such circumstances further highlight the role of the main determinants of infection and the importance of additional preventive measures, especially PPE use, in minimizing the risk of infection for both unvaccinated and vaccinated subjects.

A detailed assessment of determinants of SARS-CoV-2 infection among unvaccinated HCWs, including the protection conferred by PPE, based on high-quality data and a proper methodology would inform prevention strategies in vaccinated subjects. We used the data on over 30,000 unvaccinated HCWs from 10 cohorts of HCWs to investigate the determinants of infection and the effectiveness of PPE worn by those who reported close contact with a confirmed SARS-CoV-2 case.

2. Methods

We use data from one cohort of HCWs employed in university hospitals and public health agencies from France (Paris), eight cohorts from Italy (Bologna, Brescia, Modena, Padua, Perugia, Trieste, Turin, and Verona), and one cohort from Romania (multicenter) to study the determinants of SARS-CoV-2 infection before vaccination, i.e., in the period March 2020-January 2021. Data on sociodemographic characteristics, PCR testing results, circumstances of contact with SARS-CoV-2 cases, symptoms, and use of PPEs were abstracted from medical surveillance records or collected using questionnaires. The PCR tests have been applied in screening surveillance, after a high-risk contact, or in case of symptoms onset. Both occupational and non-occupational sources of contact were considered.

The selected cohort characteristics (N=37,881, giving rise to 3,579 cases) included in the present analysis are described in Table 1.

These cohorts were mainly assembled during the first wave of the epidemic (March-July 2020) and are now included in the prospective follow-up. Data from the individual cohorts were harmonized; for several cohorts, de-identified data were pooled and analyzed centrally, for the others, harmonized data were analyzed at the local center.

The outcome of this analysis was infection with SARS-CoV-2 before vaccination, diagnosed with a positive PCR test. We first conducted a descriptive analysis of the outcome and explanatory variables.

Table 1. Characteristics of the cohorts of HCWs included in the analysis.

	Paris	Bologna	Brescia	Modena	Padua	Perugia	Turin	Trieste	Verona	Romania - Multicenter
N (%)	283 (0.75%)	1,579 (4.17%)	1,757 (6.63%)	5,922 (15.63%)	8,314 (21.95%)	3,196 (8.44%)	2,952 (7.79%)	4,397 (11.61%)	7,638 (20.16%)	1,843 (4.86%)
Positive cases	25 (8.83%)	70 (4.43%)	324 (18.45%)	595 (10.05%)	696 (8.37%)	164 (5.13%)	144 (4.88%)	462 (10.51%)	797 (10.43%)	302 (16.39%)
Institutions	Public hospital	Public hospitals and USL of Bologna	Public hospitals and USL of Brescia	University Hospital of Modena	University Hospital of Padua	Perugia's General Hospital	University Hospital of Turin	University Hospital of Trieste	University Hospital of Verona	Public health authorities & institutes, GPs, and hospitals
Source of data	PPEC	OHS records	OHS records	OHS records	OHS records; regional database	OHS records	OHS records	OHS records	OHS records; regional database	Active recruitment
From	Mar 2020	Mar 2020	Apr 2020	Mar 2020	Mar 2020	Mar 2020	Mar 2020	Mar 2020	Mar 2020	Aug 2020
To	Dec 2020	Jan 2021	Jan 2021	Dec 2020	Dec 2020	Dec 2020	Aug 2020	Dec 2020	Dec 2020	Jan 2021

PPEC = Prospective post-exposure cohort; OHS = Occupational health surveillance.

Subsequently, we conducted cohort-specific logistic regression analyses with the PCR result as a dependent variable to estimate odds ratios (OR) and the corresponding 95% Confidence Intervals (CI). In the second step, cohort-specific results were combined using random-effects meta-analyses; heterogeneity between cohort-specific results was tested using the I^2 method [15]. We conducted additional analyses on the use of PPEs separately for the first (March 2020-July 2020) and the second wave of the pandemic (August 2020-January 2021). The statistical package STATA V. 16.1 was used for the analysis.

The study was part of the Orchestra project. It was approved by the Institutional Review Boards of the Italian Medicine Agency (AIFA) and the Italian National Institute of Infectious Diseases "L. Spallanzani". Local Institutional Review Boards approved individual cohorts as appropriate.

3. Results

A total of 38,793 HCWs from the ten cohorts were included in the analyses. The distribution of subjects in each cohort according to the outcome, the explanatory variables, the distribution of symptoms, and the use of PPE according to the outcome are provided in Table 2.

Overall, 3,716 cohort members were infected during the study period (9.58%); this proportion varied from 4.43% to 17.29% in the individual cohorts.

The results of the meta-analysis on determinants of infection before vaccination are reported in Table 3, and the corresponding results for the individual cohorts are reported in Supplementary Table 1.

Infection was not associated with the sex, age, or job title of HCWs. Among the symptoms, fever, ache, fatigue, anosmia, cough, and ageusia were strongly associated with SARS-CoV-2 infection. In particular, the OR of infection was 4.63 (95% CI 1.70-12.65) for those with fever compared to those without it. The results also showed that those who did not report any contact with SARS-CoV-2 cases had a higher chance of being infected than those who reported contact with colleagues (OR=7.08; 95% CI 2.25-22.32) (Table 3).

The results of the analysis on the use of PPE are reported in Table 4, and the corresponding results for different waves of SARS-CoV-2 infection are reported in Supplementary Table 2.

Use of surgical masks (OR=0.51; 95% CI 0.39-0.65), and FFP2/FFP3 masks (OR=0.43; 95% CI 0.32-0.57) showed significant protection against SARS-CoV-2 infection. However, eye protection/face shield use did not appear to be protective (OR=1.65; 95% CI 1.22-2.24). FFP2/FFP3 mask use was more protective during the second wave of the SARS-CoV-2 pandemic (August 2020-January 2021, OR=0.27; 95% CI 0.17-0.43) than during the first wave.

4. Discussion

Among more than 38,000 HCWs, we reported results on more than 3,700 un-vaccinated HCWs who tested positive for SARS-CoV-2 between March 2020 and January 2021. Sex, age, and job title were not associated with infection, and HCWs assigned to COVID-19 units were not at higher risk of infection. Anosmia was the most predictive symptom, and mask use was the most effective PPE in reducing the risk of infection.

The heterogeneity in infection rates found among HCWs in these institutions demonstrates the wide range of circumstances of infection among hospitals, even within a single country. Such variability is unsurprising, as local policies differed significantly between institutions and have altered fast throughout the pandemic as PPE access, capacity, and understanding of transmission have shifted.

In fact, throughout much of 2020, the World Health Organization (WHO) held tight to the idea that SARS-CoV-2 spreads through relatively large "respiratory" droplets that are expelled by infected people while coughing, sneezing, or speaking and stressed the importance of washing hands and disinfecting surfaces. It took many months for the Agency to acknowledge that the virus transmission is sustained by aerosols that can spread widely and linger in the air [18]. Higher SARS-CoV-2 infection rates were usually seen in centers from areas with corresponding higher population rates [19]. In particular, observations from Spain showed that the epidemic dynamic among HCWs closely followed that in the community, arguing against significant

Table 2. Selected characteristics of HCWs included in the analysis.

	Paris (%)	Bologna (%)	Brescia (%)	Modena (%)	Padua (%)	Perugia (%)	Turin (%)	Trieste (%)	Verona (%)	Romania-Multicenter (%)
Sex										
Men	28.3%	29.5%	22.0%	29.3%	31.3%	35.1%	29.5%	31.1%	30.8%	17.5%
Women	71.7%	70.5%	78.0%	70.7%	68.7%	64.9%	70.5%	68.9%	69.2%	82.5%
Age group										
18-29	26.1%	13.5%	12.4%	18.3%	14.7%	3.5%	11.2%	6.8%	17.7%	6.4%
30-39	33.9%	30.8%	21.1%	27.4%	23.6%	24.7%	18.4%	17.9%	26.8%	12.7%
40-49	20.9%	25.8%	28.1%	21.7%	20.5%	19.9%	28.2%	26.2%	18.7%	3.1%
50+	19.1%	29.9%	38.4%	32.6%	41.2%	51.9%	42.2%	49.2%	36.7%	50.2%
Job title										
Administration	12.3%	1.3%	7.16%	5.3%	8.2%	6.8%	5.1%	6.2%	7.9%	3.1%
Physician	35.9%	20.6%	22.3%	31.2%	33.5%	29.2%	29.6%	14.3%	34.6%	72.2%
Nurse	29.5%	28.8%	48.8%	35.8%	35.95	37.5%	40.4%	40.7%	33.6%	13.3%
Technician	0.0%	2.5%	9.7%	3.4%	6.6%	12.3%	0.0%	5.2%	8.7%	9.8%
Other HCW	1.6%	46.7%	11.9%	24.4%	15.8%	14.3%	24.8%	33.6%	15.3%	22.3%
Source of contact										
Colleague	57.6%	48.8%	51.9%				56.0%			
Outside workplace	11.3%	4.2%	8.1%				5.1%			
No contact (screening)	0.0%	0.4%	14.2%				0.0%			
Patients	31.1%	46.5%	25.8%				38.9%			
High-risk contact with COVID cases										
No	0.0%		83.9%				0.0%			81.3%
Yes	100.0%		16.1%				100.0%			18.7%
Dedicated to COVID patients										
No	64.7%		54%				92.9%			
Yes	35.3%		46%				7.1%			
Symptoms										
No symptom	40.1%	83.7%	57.9%				41.9%			6.0%*
At least one symptom	59.9%	16.3%	42.1%				58.1%			94.0%*

Table 2 (*Continued*)

	Paris (%)	Bologna (%)	Brescia (%)	Modena (%)	Padua (%)	Perugia (%)	Turin (%)	Trieste (%)	Verona (%)	Romania-Multicenter (%)
Fever	10.9%		9.4%				2.3%			40.1%*
Dyspnoea	7.7%		5.5%				1.0%			25.8%*
Diarrhoea	14.2%		6.7%				2.2%			17.2%*
Sore throat	15%		27.3%				6.5%			34.4%*
Headache	36.1%		27.7%				1.5%			47.7%*
Myalgia / arthralgia	20.1%		22.8%							46.7%*
Fatigue / malaise	30.3%		15.4%				0.9%			68.9%*
Anosmia or hyposmia	5.5%		0.4%				0.4%			52.0%*
Cough	20.4%		24.0%				10.0%			42.4%*
Ageusia or hypogeusia			2.0%				0.5%			42.0%*
Other symptoms	30.3%		0.6%							
Use of PPE										
Surgical masks	0%	70.3%	27.4%				72.2%			93.3%**
FFP2/FFP3 masks	0%	24.2%	41.3%				7.5%			68.2%**
Eye protection/Face shield		3.0%	7.8%				16.9%			70.8%**
Isolation/disposable gowns		4.7%	8.4%				15.0%			58.9%**
Gloves		28.2%	27.8%				43.9%			86.4%**

** Adjusted for gender and age (categorical).*

*** Adjusted for gender, age (categorical), and job title.*

CI, confidence interval; OR, odds ratio; Ref, reference category; empty cell, not available.

Table 3. Determinants of infection before vaccination – Results of the meta-analysis.

Characteristic [Centers included in the pooled analysis]	OR (95% CI)	I^2
Sex [All]		
Men	Ref	
Women	1.00 (0.92-1.09)	29.1%
Age [All]		
10-yr increase	0.96 (0.89-1.05)	88.1%
Job Title [All] *		
Administration	Ref	
Physician	1.00 (0.82-1.21)	35.0%
Nurse	1.21 (0.87-1.69)	79.7%
Technician	0.98 (0.80-1.20)	13.9%
Other HCW	1.35 (0.93-1.94)	78.0%
Source of contact [Fr-Pa, It-Bo, It-Br, It-To] **		
Colleague	Ref	
Family/friends or outside the workplace	2.07 (0.78-5.50)	60.4%
Patients	1.28 (0.63-5.29)	87.9%
Unknown (screening, symptomatic HCW)	7.08 (2.25-22.32)	57.9%
High-risk contact with COVID cases [It-Br, Ro-Mc] **		
No	Ref	
Yes	1.17 (0.89-1.53)	0.0%
Dedicated to COVID patients [Fr-Pa, It-Br, It-To] **		
No	Ref	
Yes	1.18 (0.95-1.46)	0.0%
Symptoms [Fr-Pa, It-Br, It-To] *		
No symptom	Ref	
Fever	4.63 (1.70-12.65)	85.7%
Dyspnoea	1.45 (0.31-6.82)	85.3%
Diarrhoea	0.58 (0.35-0.96)	0.8%
Sore throat	0.99 (0.52-1.89)	55.9%
Headache	1.59 (0.81-3.11)	43.2%
Ache [i.e., Muscle (myalgia) and/or Joint (arthralgia)]	2.60 (1.80-3.78)	0.0%
Fatigue and/or malaise	2.77 (1.22-6.28)	50.1%
Loss of smell (Anosmia)	8.24 (3.48-19.51)	0.0%
Cough	2.61 (1.23-5.57)	85.1%
Changes or loss in taste (Ageusia)	4.41 (1.87-10.39)	0.0%

** Adjusted for gender and age (categorical).*
*** Adjusted for gender, age (categorical), and job title.*
CI, Confidence Interval; OR, odds ratio; Ref, reference category; empty cell, not available.

Table 4. Use of PPE: Results of pooled data (CI=confidence interval; OR=odds ratio, adjusted for cohort, sex, age (categorical), and job title; Ref reference category.

PPE	OR (95% CI)
Surgical masks	
No	Ref
Yes	0.51 (0.39-0.65)
FFP2/FFP3 masks	
No	Ref
Yes	0.43 (0.32-0.57)
Eye protection/Face shield	
No	Ref
Yes	1.65(1.22-2.24)
Isolation/disposable gowns	
No	Ref
Yes	1.93 (1.43-2.60)
Gloves	
No	Ref
Yes	1.27 (0.98-1.66)

occupational transmission [20]. In addition, the different geographic location of the centers involved explains the different infection rates also because of the asynchronous nature of the pandemic. Especially in Italy, regions considered the epicenter of the virus spread were more involved in the first wave, while others were more affected in the following waves. Male gender and advanced age represent well-known risk factors for the severity of COVID-19 [21]. The present study did not find an increased risk of infection according to age and gender. These results align with the available literature where age does not show a clear pattern with the risk of infection, while gender findings often disagree [19, 22]. Moreover, in a seroprevalence study conducted in a large health center in Italy, age and gender were not associated with the risk of seropositivity, not even evaluating part of the cohort after five months [23].

Unlike other studies [24-26], we have not found differences in the risk of infection across HCW job titles, possibly because of the long observation period and the onset and diffusion of different SARS-CoV-2 variants with a higher infection rate [27]. Many prevalence studies, based on either PCR or serology, also reported no difference in risk of infection according to job title [23, 28]. These data partially overlap with those used in our previous publication. We suggested that the lack of a clear pattern of risk according to job categories indicates that all HCWs were at comparable risk of becoming infected, even if we consider HCWs who worked in COVID-19 departments [19], consistently with the multiple sources of exposure to SARS-CoV-2 reported by HCW, whether from infected patients or colleagues, but also with individuals outside the workplace that do not directly depend on HCW's job title.

Our analysis confirms that either surgical or FFP2/3 masks are the most effective PPE in reducing SARS-CoV-2 transmission. Scientific evidence supports their role in infection control [19, 29, 30]. Besides their mechanical barrier function, some studies [31, 32] suggest their active role in modulating viral load and boosting the immune response, especially in the pre-vaccinal period. This mechanism is similar to the so-called "variolation" process, where people susceptible to smallpox were inoculated with a small amount, causing a mild infection and subsequent immunity. In particular, we found that FFP2/FFP3 masks were more protective than surgical masks during the second wave of the COVID pandemic, which is an original result of our study. This result may be derived from two factors. First, the virus has changed, resulting in multiple variants with different physical and transmissibility properties. In this view, a recent study by Riediker et al. [33] highlighted that for Delta and Omicron variants, surgical masks were not effective in most public settings, while correctly fitted FFP2 respirators still provided sufficient protection. Several other studies on SARS-CoV-2 variants suggest that higher viral load and increased infectivity were likely to contribute to the rapid spread of the Delta variant of SARS-CoV-2, the dominant variant during the second wave of the epidemic [34]. The Delta variant seems more stable in aerosol than the original form of the virus, which may explain the greater relevance of face-filtered masks compared to surgical ones. On the other hand, another critical aspect is that during the second wave of the epidemic, PPE shortage was no longer an issue, and mask-wearing was strongly

required, so the lack of compliance with the rules by the HCW would be less justified.

On the contrary, an initial reading of our results indicates that using facial shields, disposable gowns, and gloves is associated with an increased risk of infection. This counterintuitive finding is attributable to the extensive use of these PPEs, mainly in departments with higher infection rates. These results are confirmed by the increased risk of infections for HCWs dedicated to COVID-19 patients.

Notable is the strong association we detected between increased risk of infection and fevers, muscular or joint aches, anosmia, and ageusia. Those findings are consistent with the scientific literature on other populations of COVID-19 patients [35, 36].

The large sample size and the collection of sociodemographic information from occupational health records or regional databases are strengths of our study. However, our analysis suffers from some limitations, including the retrospective nature of the data and the different health surveillance protocols throughout our cohorts. In particular, variations in PPE access, reuse, and types offered between centers raise the possibility of measurement error, which could have masked our ability to detect an association between PPE use and SARS-CoV-2 infection. In addition, data sources and symptoms' classification varied among cohorts. As shown in Table 2, not all cohorts recorded data concerning the type/risk of contact and the use of PPE. Also, some centers conducted statistical analyses internally while others shared raw data. This heterogeneity was partially resolved by subsequent harmonization of the data. Nevertheless, these differences may have affected the generalizability of the results.

Moreover, the multicentric nature of the study, while significantly increasing the size of the analyzed sample, makes it more difficult to compare and may have partially affected the accuracy of the infection rate data. Furthermore, because we did not compare the viruses of cases and contacts, we cannot state with certainty which contact caused the infection.

5. Conclusions

In this study, we present findings that evaluate predictors of SARS-CoV-2 transmission, which are important to limit the risk of infection inside and outside the workplace. Mask wear should be compulsory in hospital settings to ensure the safety of both HCWs and patients. Even among vaccinated subjects, PPEs remain an important set of instruments, and proper usage should be emphasized. It would be desirable to conduct more research on the combined usage of PPEs under various SARS-CoV-2 transmission scenarios. Models of prospective public health actions that could have prevented the epidemic and early recommendations for using surgical masks would be extremely useful in the future.

Supplementary Materials: The following are available: Supplementary Tables 1A, 1B, and 2.

Funding: The Orchestra project is funded by the European Commission, Horizon 2020 Program, Grant Agreement No. 101016167. The cohort from Verona is funded by the Regional Health Authority (Azienda Zero), Veneto Region, Italy.

Resource Sharing Statement: Data sharing will occur according to the guidelines established within the Orchestra project (www.orchestra-cohort.eu).

Acknowledgments: The Verona group thanks to the General Management, Medical Management, and all personnel of the Units of Occupational Health, Laboratory Medicine and Microbiology and of University Hospital of Verona and all personnel of the Unit of Epidemiology and Medical Statistics, University of Verona, for their constant support and generous contributions.

Declaration of Interest: The authors declare no conflicts of interest.

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APPENDIX

SUPPLEMENTARY Table 1a. Determinants of infection before vaccination – results by cohort.

	France-Paris	Italy-Bologna	Italy- Brescia	Italy-Modena	Italy-Padua
	OR (95% CI)	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
Sex					
Men	Ref	Ref	Ref	Ref	Ref
Women	0.56 (0.24-1.34)	1.12 (0.67- 1.88)	0.91 (0.75-1.11)	0.86 (0.73- 1.01)	1.06 (0.91- 1.23)
Age					
10-yr increase	1.00 (0.68-1.44)	1.13 (0.89- 1.43)	1.07 (0.99-1.17)	1.01 (0.95- 1.07)	0.97 (0.92- 1.03)
Job Title *					
Administration	Ref	Ref	Ref	Ref	Ref
Physician	0.84 (0.22-5.63)	0.71 (0.35- 1.40)	0.91 (0.63-1.31)	2.11 (1.26- 3.54)	1.12 (0.80- 1.56)
Nurse	0.80 (0.19-4.06)	1.06 (0.59- 1.90)	0.74 (0.53-1.03)	3.59 (2.17- 5.96)	1.57 (1.15-2.14)
Technician		1.02 (0.23- 4.57)	0.89 (0.59-1.33)	1.80 (0.91- 3.54)	1.17 (0.77- 1.77)
Other HCW	1.12 (0.27-5.64)		0.77 (0.49-1.21)	2.63 (1.56- 4.43)	2.30 (1.66- 3.18)
Source of contact **					
Colleague	Ref	Ref	Ref	Ref	Ref
Family/friends or outside workplace		1.02 (0.29-3.59)	3.02 (2.10-4.33)		
No opportunity of contact		17.34 (3.48- 86.41)	4.93 (3.82-6.38)		
Patients	1.97 (0.74-5.29)	0.96 (0.51-1.80)	2.30 (1.79-2.95)		
High-risk contact with COVID cases **					
No	Ref	Ref	Ref	Ref	Ref
Yes			1.05 (0.66-1.65)		
Dedicated to COVID patients **					
No	Ref	Ref	Ref	Ref	Ref
Yes	2.16 (0.77-6.40)		1.13 (0.90-1.43)		
Symptoms*					
No symptom	Ref	Ref	Ref	Ref	Ref
Fever	3.42 (0.90-13.46)		2.71 (1.70-4.30)		
Dyspnoea	3.16 (0.68-14.88)		0.41 (0.19-0.85)		
Diarrhoea	0.79 (0.19-2.85)		0.48 (0.26-0.86)		
Sore throat	1.75 (0.40-7.60)		0.66 (0.45-0.98)		
Headache	0.63 (0.15-2.34)		1.56 (1.07-2.28)		
Ache (i.e., Muscle ache (myalgia) and/ or Joint ache (arthralgia))	1.95 (0.48-8.38)		2.63 (1.78-3.88)		
Fatigue and/or malaise	1.47 (0.32-6.33)		2.05 (1.067-3.94)		

	France-Paris	Italy-Bologna	Italy- Brescia	Italy-Modena	Italy-Padua
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Loss of smell (Anosmia)	14.50 (3.21-19.51)				
Cough	0.98 (0.25-3.43)		2.21 (1.55-3.16)		
Changes or loss in taste (Ageusia)			4.81 (1.62-14.29)		
Other symptoms	6.88 (1.89-29.90)				

** Adjusted for gender and age (categorical).*
*** Adjusted for gender, age (categorical), and job title.*
CI, confidence interval; OR, odds ratio; Ref, reference category; empty cell, not available.

Supplementary Table 1b. Determinants of infection before vaccination – results by cohort.

	Italy-Perugia	Italy-Turin	Italy-Trieste	Italy-Verona	Romania-Multicenter
Characteristics*	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
Sex					
Men	Ref	Ref	Ref	Ref	Ref
Women	0.93 (0.73- 1.20)	0.92 (0.66-1.28)	1.00 (0.83- 1.21)	1.18 (1.02- 1.37)	1.14 (0.81-1.59)
Age					
10-yr increase	0.89 (0.80- 0.99)	0.97 (0.84-1.12)	0.81 (0.75- 0.88)	1.13 (1.07- 1.19)	0.78 (0.70-0.87)
Job Title *					
Administration	Ref	Ref	Ref	Ref	Ref
Physician	1.15 (0.66- 2.03)	0.79 (0.39-1.60)	0.69 (0.45- 1.05)	1.05 (0.77- 1.42)	0.79 (0.39-1.57)
Nurse	0.93 (0.53- 1.63)	0.72 (0.39-1.41)	0.84 (0.58- 1.22)	1.85 (1.39- 2.47)	1.30 (0.62-2.73)
Technician	0.91 (0.48- 1.72)		0.64 (0.37- 1.13)	1.08 (0.75- 1.55)	0.59 (0.27-1.32)
Other HCW	1.90 (1.07- 3.38)	0.80 (0.40-1.63)	0.83 (0.57- 1.21)	1.84 (1.35- 2.50)	0.62 (0.17-2.18)
Source of contact **					
Colleague	Ref	Ref	Ref	Ref	Ref
Outside workplace					
No contact					
Patients		0.67 (0.43-1.05)			
High-risk contact with COVID cases **					
No	Ref	Ref	Ref	Ref	Ref
Yes					1.24 (0.88-1.72)
Dedicated to COVID patients **					
No	Ref	Ref	Ref	Ref	Ref
Yes		1.28 (0.70-2.32)			
Symptoms*					
No symptom	Ref	Ref	Ref	Ref	Ref
Fever		9.88 (5.87-16.65)			

Table S1b (*Continued*)

Characteristics*	Italy-Perugia OR (95% CI)	Italy-Turin OR (95% CI)	Italy-Trieste OR (95% CI)	Italy-Verona OR (95% CI)	Romania-Multicenter OR (95% CI)
Dyspnoea		3.04 (1.16-8.00)			
Diarrhoea		1.22 (0.34-4.29)			
Sore throat		1.42 (0.70-2.90)			
Headache		3.36 (1.11-10.17)			
Myalgia/ arthralgia)					
Fatigue/malaise		6.35 (2.29-17.61)			
Anosmia		5.87 (1.83-18.80)			
Cough		4.95 (3.48-7.03)			
Ageusia		2.89 (0.66-12.66)			
Other symptoms					

** Adjusted for gender and age (categorical).*
*** Adjusted for gender, age (categorical), and job title.*
CI, confidence interval; OR, odds ratio; Ref, reference category; empty cell, not available.

Supplementary Table 2. Use of PPE– results by pandemic wave.

	1st wave Brescia and Turin	2nd wave Bologna, Brescia, and Turin
	OR (95% CI)	OR (95% CI)
Surgical masks		
No	Ref	Ref
Yes	0.52 (0.38-0.71)	0.58 (0.37-0.91)
FFP2/FFP3 masks		
No	Ref	Ref
Yes	0.90 (0.60-1.36)	0.27 (0.17-0.43)
Eye protection/Face shield		
No	Ref	Ref
Yes	1.03 (0.72-1.48)	4.25 (2.13-8.50)
Isolation/disposable gowns		
No	Ref	Ref
Yes	1.03 (0.72-1.48)	1.97 (1.05-3.69)
Gloves		
No	Ref	Ref
Yes	1.37 (0.99-1.89)	1.12 (0.66-1.90)
Centers		
Italy-Bologna		Ref
Italy-Brescia	4.24 (3.09-5.81)	6.44 (3.91-10.59)
Italy-Turin	Ref	0.61 (0.08-4.72)

CI, confidence interval; OR, odds ratio; Ref, reference category; empty cell, not available.