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Factors associated with SARS-CoV-2 infection among healthcare workers: a European multicentre cohort study, May 2021–April 2024

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Abstract

Background Healthcare workers (HCWs) faced increased SARS-CoV-2 infection risk. We aimed to identify factors associated with SARS-CoV-2 infection in HCWs and assess how their association with infection changed over time to prepare for future similar events.

Methods We conducted a cohort study among HCWs from 18 European hospitals that completed weekly questionnaires and tested weekly/fortnightly by PCR. We defined separate cohorts for pre-Omicron (May 2021–December 2021), pandemic Omicron (December 2021–April 2023), and post-pandemic Omicron (September 2023–April 2024) periods. Using Cox proportional hazards models, we estimated adjusted hazard ratios (aHRs) for associations between each exposure and SARS-CoV-2 infection, adjusting for age, sex, underlying conditions, and hospital.

Results We included 1395, 2056, and 1254 HCWs in the three periods. Median age was 44 years, and 2597 (80%) were female, 740 (22%) medical doctors, 1399 (42%) nurses, 391 (12%) administrative personnel, 113 (3%) ancillary personnel, and 612 (18%) worked in other roles. Compared to medical doctors, ancillary personnel presented the highest risk pre-Omicron (aHR 3.86, 95% CI [1.30, 11.47]). Household contact was the strongest risk factor pre-Omicron (aHR 4.05 95% CI [1.78, 9.19]) but decreased over time.

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Conclusions Household exposure and occupational role were key risk factors, but their effect size decreased over time. Infection prevention strategies should be regularly updated, extending beyond clinical staff and considering household exposure, should similar events occur.

Clinical trial number Not applicable.

Keywords SARS-CoV-2, Healthcare workers, Occupational exposure, Infection prevention and control, Risk factors

Introduction

Healthcare workers (HCWs) were at the forefront of the coronavirus disease 2019 (COVID-19) pandemic, facing high rates of severe respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, estimated around 10% after the first wave and over 20% after the emergence of viral variants [1, 2]. The risk of infection among HCWs changed over the course of the COVID-19 pandemic due to improved access to personal protective equipment (PPE), updated infection prevention and control (IPC) guidelines, the emergence of more transmissible viral variants, increasing immunity from vaccination or prior infection, and changes in risk perception and behaviours [1, 3–7]. During the SARS-CoV-2 pandemic, protecting HCWs from infection was crucial not only to maintain healthcare system capacity but also to prevent hospital-associated transmission from HCWs to vulnerable patients. Therefore, identifying risk factors for infection among HCWs was important for workplace safety policies and IPC policy development [8], and the evolution of their association with infection over time could inform development of such policies.

SARS-CoV-2 infection risk depends on occupational, community, and individual susceptibility factors. Early HCW studies mainly focused on the first pandemic phase, when the primary concern was exposure to a novel pathogen in the healthcare setting [1, 2, 9, 10]. These studies mainly assessed the effectiveness of PPE and IPC measures and risks linked to direct COVID-19 patient care or COVID-19 wards. Reported occupational risk factors included direct patient contact, performance of aerosol-generating procedures, inadequate/insufficient PPE, and poor IPC adherence [1, 2, 5, 9, 11]. Other risk factors among HCWs, including female sex, inadequate hand hygiene, and assisting patients with activities of daily living, presented inconsistent findings [5, 9, 11–13]. With the introduction of COVID-19 vaccines, research priorities shifted towards evaluating their protective effects among HCWs [6, 14].

Significant gaps remained in understanding how infection risk factors evolve over time and across different phases of a large-scale health emergency. The emergence of the Omicron variant, with high transmissibility and immune evasion [15, 16], fundamentally altered infection dynamics, necessitating a reassessment of established risk factors. Moreover, as HCWs gained immunity through vaccination and prior infections [17, 18] and non-pharmaceutical interventions in the community were relaxed [19, 20], the relative importance of community versus occupational exposures likely shifted [4, 5, 12]. Although one study reported a transition from predominantly clinical to community-related risk factors during Omicron waves [5], little evidence is available on how risk profiles change in later phases of a prolonged epidemic or how such insights can inform preparedness for future similar events.

Between May 2021 and April 2024, the European Centre for Prevention and Control (ECDC) set up a cohort of HCWs to monitor COVID-19 vaccine effectiveness. Using data from this multicentre prospective cohort, we assessed associations between occupational, community, and individual exposures and SARS-CoV-2 infection among hospital-based HCWs and examined how these associations developed over time. By identifying both persistent and time-varying determinants of infection risk, findings from this study shall inform infection prevention strategies and guide policies to protect essential healthcare personnel should a similar emergency happen.

Methods

Study design

This analysis study was conducted within the Vaccine Effectiveness, Burden and Impact Studies (VEBIS) HCW study framework. VEBIS-HCW was a prospective, multicentre cohort study conducted in HCWs from 18 hospitals in nine European countries (Croatia, Estonia, Greece, Ireland, Italy, Latvia, Poland, Romania, and Spain). Study procedures have been described in detail in the VEBIS HCW protocol [21]. The study protocol evolved during the course of the study; protocol modifications are detailed in the Supplementary Material.

Study population and follow-up

All HCWs in participating hospitals were invited to participate, regardless of occupational role. The study was conducted in three periods: pre-Omicron (May 3, 2021 – December 14, 2021), pandemic Omicron (December 15, 2021 – May 2, 2023), and post-pandemic Omicron (September 1, 2023 – April 30, 2024). Hospital participation was dynamic, with varying start and end dates (Figure S1). Following recommendations for a seasonal approach

to SARS-CoV-2 surveillance and COVID-19 vaccination [22], we excluded the 2023 summer season.

We excluded HCWs who missed the enrolment questionnaire, did not complete any follow-up questionnaire, were never PCR-tested during follow-up or had missing age or sex. Additionally, participants who had inconsistent vaccination dates (e.g. a second dose recorded before the first), discordant testing results (i.e. seroconversion without a positive PCR test), or reported immunodeficiencies were not included in this analysis. In addition, the following person-time was excluded from the analysis: (1) person-time within 60 days after a SARS-CoV-2 infection in a previous period and (2) virological testing gaps, defined as ≥28 days without testing and no filled questionnaire, or ≥42 days without testing but with at least one questionnaire. Participants were censored separately for each analysis period at the first positive SARS-CoV-2 RT-PCR test, loss to follow-up, or the end of the period.

Data collection

Questionnaires

At enrolment, HCWs reported demographics, medical history including prior SARS-CoV-2 infections, vaccinations, underlying conditions, and occupational and community-related risk factors and behaviours. Weekly follow-up questionnaires collected time-varying data on symptoms, vaccinations, potential workplace and community exposures, and any SARS-CoV-2 infections diagnosed outside of the study. Due to changing recommendations for non-pharmaceutical interventions, social distancing variables were not collected during the post-pandemic Omicron period. Data were collected using the Voozanoo platform[1].

Laboratory and testing procedures

Upon enrolment, participants provided biological samples for SARS-CoV-2 detection by RT-PCR. During follow-up, depending on the site, participants provided either saliva samples on a weekly basis or naso-/oropharyngeal swabs on weekly/fortnightly basis. In addition to routine testing, RT-PCR testing was also conducted after reported symptoms, household or workplace exposure, or to confirm positive results from outside the study.

Definitions

The outcome was PCR-confirmed SARS-CoV-2 infection, detected either through study testing or confirmed external testing reported in follow-up questionnaires.

The primary exposures of interest were occupational and community risk factors. Occupational risk factors included occupational role, patient-facing status, self-reported adherence to IPC practices (categorised as always vs. not always), participation in aerosol-generating procedures, and contact with COVID-19 cases in the hospital (patients and coworkers). Community risk factors encompassed contact with COVID-19 cases at home and adherence to protective behaviours, such as physical distancing and mask-wearing. Adjustment covariates included individual susceptibility factors (sex, age, underlying chronic conditions) and stratification by hospital to account for differences between study sites. We also assessed adjustment for immunity variables (time since last COVID-19 vaccine booster dose and since last infection) in sensitivity analyses. Vaccination was assessed as time since last booster dose since almost all HCWs had received the primary vaccination course at the start of vaccine availability.

Time-varying exposures, included participation in aerosol-generating procedures, contact with COVID-19 cases at home or in the hospital, community behaviours, and time elapsed since the last infection (up to one year or more than one year) and the last booster dose (7–90 days, 91–180 days, >180 days). All other variables were only assessed in the enrolment questionnaires at the start of each period.

We conducted a complete case analysis. If variables collected at enrolment were missing, participants were excluded from models using the respective variables. For missing time-varying variables, the last observation was carried forward.

Statistical analysis

Descriptive statistics

In descriptive analyses, we summarised the number and percentage of HCWs contributing person-time in each exposure and covariate category, stratified by analysis period and infection status at the end of the period. For all variables, we described the status at the start of the period.

Time-to-event models

For each exposure and period, we separately estimated hazard ratios (HRs) and 95% confidence intervals (CIs) using Cox proportional hazards models with calendar time as the time scale and hospital as a stratification variable, to account for hospital-specific variation. We fit period-stratified models (i.e., one model per period) to allow for different confounding structures and underlying hazard functions by period. First, we fitted crude models including only the exposure and hospital as a stratification factor since it violated the proportional hazards assumption. Next, we fitted adjusted models, adjusting for age, sex, and underlying conditions, and stratifying by hospital. Models evaluating IPC variables were restricted

[1] https://www.epiconcept.fr/en/custom-projects/voozanoo-epicraft-technical-base/voozanoo-documentation.

to medical doctors, nurses, and nurse assistants. The proportional hazards assumption was tested using Schoenfeld residuals. To assess the effects of variables of interest independent of HCWs' immunity status, we conducted sensitivity analyses including previous infection and previous booster vaccination as adjustment variables. We also conducted a sensitivity analysis fitting models with an interaction between the main exposure term and period instead of stratifying by period. All analyses were performed in R version 4.4.2 [23], using the 'survival' package [24].

Ethical statement

The planning, conduct and reporting of the current study were in line with the Declaration of Helsinki (2013 revision). Written informed consent was obtained from all participants at enrolment, and all local ethics committees approved the study.

Results

Descriptive statistics

Of the 3,480 HCW enrolled into the VEBIS-HCW study, 227 were excluded, leaving 3253 for the analysis (Fig. 1): 1395 during the pre-Omicron period (122140 person-days), 2056 HCWs during pandemic Omicron (241255 person-days), and 1254 HCWs during post-pandemic Omicron (133617 person-days). Participants could be included in multiple periods. We recorded 53 PCR-confirmed SARS-CoV-2 infections pre-Omicron period, 600 during pandemic Omicron, and 249 during post-pandemic Omicron.

Of participating HCWs, 2597 (80%) were female, 2201 (67%) were under 50 years, and 895 (27%) had at least one underlying health condition. Most HCWs (2730, 84%) had patient-facing roles and 2139 (66%) clinical roles: 740 (22%) medical doctors and 1399 (42%) nurses/nurse assistants. The composition of the study population according to role was similar across periods (Table 1). More than 75% of clinical HCWs reported always adhering to IPC procedures (Table S1). HCWs more frequently reported workplace than household contact with COVID-19 cases (1336, 39% vs. 370, 11%), and contact reports increased across periods for both settings (hospital: 24%, 39%, 41%; home: 5%, 9%, 11%, Table 1 and Figure S2). Protective behaviours such as indoor mask use (1277, 92%), avoiding gatherings (693, 50%), and limiting use of public transportation (818, 59%) were common pre-Omicron but declined during Omicron (58%, 37%, and 50%, Table S1 and Figure S2).

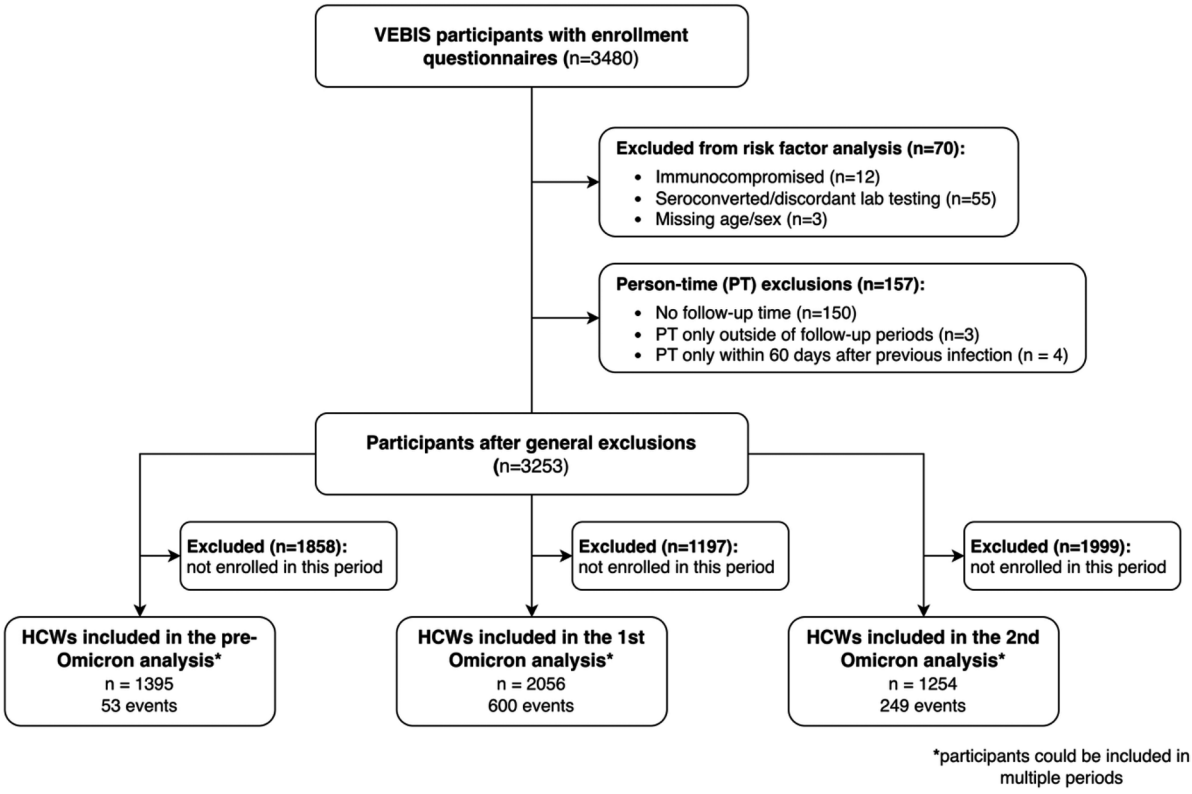


Fig. 1 Flowchart of participant inclusion in the three study periods, VEBIS-HCW European multi-centre COVID-19 study, May 2021–April 2024. Participants could be included into one or multiple periods. HCW healthcare workers, PT person time, VEBIS Vaccine Effectiveness, Burden, and Impact studies

Table 1 Description of included HCWs at the start of each study period, according to infection status at the end of the period, VEBIS-HCW European multi-centre COVID-19 study, May 2021–April 2024

Category	Pre-Omicron period (*N* = 1395)		Pandemic Omicron period (*N* = 2056)		Post-pandemic Omicron period (*N* = 1254)	
	Not infected (*n* = 1342, 96.2%)	Infected (*n* = 53, 3.8%)	Not infected (*n* = 1456, 70.8%)	Infected (*n* = 600, 19.2%)	Not infected (*n* = 1005, 80.1%)	Infected (*n* = 249, 19.9%)
Person-days	118,494	3,646	187,378	53,877	120,386	13,231
Age						
18–49	845 (63%)	35 (66%)	993 (68%)	412 (69%)	657 (65%)	158 (63%)
≥ 50	497 (37%)	18 (34%)	463 (32%)	188 (31%)	348 (35%)	91 (37%)
Sex						
Female	981 (73%)	40 (75%)	1203 (83%)	489 (82%)	834 (83%)	214 (86%)
Male	361 (27%)	13 (25%)	253 (17%)	111 (18%)	171 (17%)	35 (14%)
Any chronic health condition						
No	974 (73%)	32 (60%)	1056 (73%)	426 (71%)	743 (74%)	162 (65%)
Yes	359 (27%)	20 (38%)	387 (27%)	170 (28%)	260 (26%)	86 (35%)
Missing	9 (1%)	1 (2%)	13 (1%)	4 (1%)	2 (0%)	1 (0%)
Time since last booster dose at start of period						
TSB 7-90d	9 (1%)	0 (0%)	380 (26%)	186 (31%)	34 (3%)	5 (2%)
TSB 91-180d	0 (0%)	0 (0%)	152 (10%)	73 (12%)	15 (1%)	0 (0%)
Never vaccinated or TSB > 180d	1333 (99%)	53 (100%)	924 (63%)	341 (57%)	956 (95%)	244 (98%)
Time since last infection at start of period						
TSLI 2–12 months	184 (14%)	1 (2%)	482 (33%)	145 (24%)	175 (17%)	30 (12%)
> TSLI 12 months or never had an infection	1158 (86%)	52 (98%)	974 (67%)	455 (76%)	830 (83%)	219 (88%)
Occupation						
Administration/ Reception	138 (10%)	8 (15%)	169 (12%)	83 (14%)	136 (14%)	41 (16%)
Allied professional	59 (4%)	4 (8%)	57 (4%)	23 (4%)	26 (3%)	8 (3%)
Ancillary	54 (4%)	7 (13%)	35 (2%)	31 (5%)	41 (4%)	9 (4%)
Medical Doctor	352 (26%)	9 (17%)	314 (22%)	103 (17%)	189 (19%)	33 (13%)
Nurse/nurse assistants	536 (40%)	18 (34%)	628 (43%)	254 (42%)	460 (46%)	118 (47%)
Laboratory	85 (6%)	3 (6%)	72 (5%)	45 (8%)	44 (4%)	14 (6%)
Other	115 (9%)	4 (8%)	152 (10%)	56 (9%)	104 (10%)	26 (10%)
Missing	3 (0%)	0 (0%)	29 (2%)	5 (1%)	5 (0%)	0 (0%)
Performing aerosol generating procedures						
No	874 (65%)	42 (79%)	1,136 (78%)	440 (73%)	868 (86%)	219 (88%)
Yes	217 (16%)	8 (15%)	215 (15%)	92 (15%)	118 (12%)	25 (10%)
Missing	251 (19%)	3 (6%)	105 (7%)	68 (11%)	19 (2%)	5 (2%)
Contact with a case in the hospital						
No	805 (60%)	39 (74%)	758 (52%)	349 (58%)	576 (57%)	149 (60%)
Yes	318 (24%)	13 (25%)	601 (41%)	196 (33%)	413 (41%)	97 (39%)
Missing	219 (16%)	1 (2%)	97 (7%)	55 (9%)	16 (2%)	3 (1%)
Contact with a case at home						
No	1,261 (94%)	48 (91%)	1,302 (89%)	544 (91%)	852 (85%)	217 (87%)
Yes	66 (5%)	5 (9%)	126 (9%)	51 (8%)	115 (11%)	25 (10%)
Missing	15 (1%)	0 (0%)	28 (2%)	5 (1%)	38 (4%)	7 (3%)

TSLI time since last infection, TSB time since last booster

Table 2 Risk and protective factors of SARS-CoV-2 infection among HCWs in the pre-Omicron period, VEBIS-HCW European multicentre COVID-19 study, May 3, 2021–December 14, 2021. The number of included HCWs in each model as well as the events and person-time are listed for the crude models. These numbers can differ from the total number of included HCWs for each period either due to missing data in the assessed variable (lower number of included HCWs) or due to HCWs being included in multiple categories over the period for time-varying exposures

Exposure	Response	*N* HCWs	*N* events	Person-time	Crude* HR (95% CI)	Adjusted** HR (95% CI)
Sex	Female	1021	40	90,165	1 (ref)	1 (ref)
	Male	374	13	31,975	1.02 (0.53; 1.95)	1.12 (0.58; 2.16)
Age groups (years)	18–49	880	35	75,035	1 (ref)	1 (ref)
	≥ 50	515	18	47,105	0.77 (0.43; 1.37)	0.68 (0.38; 1.24)
Any chronic condition	No	1006	32	86,017	1 (ref)	1 (ref)
	Yes	379	20	35,433	1.38 (0.78; 2.45)	1.47 (0.83; 2.63)
Time since last infection (TSLI)	TSLI 2–12 months	185	0	12,426	1 (ref)	1 (ref)
	> TSLI 12 months or never had an infection	1265	53	109,714	DNC	DNC
Time since last booster dose (TSB)	TSB 7–90 days	415	5	10,391	1 (ref)	1 (ref)
	TSB 91–180 days	0	0	0	DNC	DNC
	Never vaccinated or > TSB 180 days	1386	48	111,749	1.85 (0.62; 5.53)	1.82 (0.61; 5.42)
Occupational role	Medical Doctor	361	9	30,336	1 (ref)	1 (ref)
	Administration/Reception	146	8	13,973	1.88 (0.69; 5.12)	1.99 (0.71; 5.54)
	Allied professional	63	4	6428	1.54 (0.45; 5.35)	1.56 (0.45; 5.48)
	Ancillary	61	7	6155	3.6 (1.24; 10.43)	3.86 (1.3; 11.47)
	Nurse/Nurse assistants	554	18	47,439	1.25 (0.55; 2.85)	1.23 (0.52; 2.89)
	Laboratory	88	3	8315	1.32 (0.35; 4.98)	1.4 (0.36; 5.38)
	Other	119	4	9319	1.75 (0.52; 5.92)	1.83 (0.54; 6.25)
Patient-facing occupation	No	258	5	23,081	1 (ref)	1 (ref)
	Yes	1096	47	95,708	1.98 (0.78; 5.07)	1.87 (0.73; 4.83)
Following IPC: Hand hygiene	Not always	68	0	7022	1 (ref)	1 (ref)
	Always	358	15	32,520	DNC	DNC
Following IPC: Patient contact	Not always	54	0	6141	1 (ref)	1 (ref)
	Always	338	10	30,168	DNC	DNC
Following IPC: Personal protective equipment	Not always	142	6	13,641	1 (ref)	1 (ref)
	Always	751	20	62,469	0.8 (0.3; 2.11)	0.78 (0.29; 2.07)
Aerosol generating procedures	No	973	41	80,673	1 (ref)	1 (ref)
	Yes	263	9	20,287	0.89 (0.43; 1.87)	0.88 (0.42; 1.86)
Contact with a case in the hospital	No	871	36	74,641	1 (ref)	1 (ref)
	Yes	416	16	28,766	1.07 (0.58; 1.99)	0.99 (0.53; 1.87)
Contact with a case at home	No	1372	45	116,545	1 (ref)	1 (ref)
	Yes	185	8	4355	4 (1.77; 9.03)	4.05 (1.78; 9.19)
Frequency of taking public transit in the last week	Never	1058	31	68,511	1 (ref)	1 (ref)
	One to two times	564	7	19,894	0.67 (0.28; 1.6)	0.69 (0.29; 1.66)
	Three or more	564	15	33,394	0.88 (0.43; 1.79)	0.88 (0.43; 1.82)
Masking indoors	Always/Often	1351	52	105,035	1 (ref)	1 (ref)
	Sometimes/Never/Rarely	388	1	15,730	DNC	DNC
Attending gatherings	Never	1046	28	59,384	1 (ref)	1 (ref)
	One to two times	1080	20	49,313	0.88 (0.49; 1.58)	0.82 (0.45; 1.5)
	Three or more	473	4	12,767	0.66 (0.22; 1.91)	0.63 (0.22; 1.86)
Keeping distance indoors	Always/Often	1172	36	76,802	1 (ref)	1 (ref)
	Sometimes/Never/Rarely	910	16	44,978	0.94 (0.5; 1.78)	0.94 (0.49; 1.78)

Table 2 (continued)

Exposure	Response	*N* HCWs	*N* events	Person-time	Crude* HR (95% CI)	Adjusted** HR (95% CI)
Having visitors from outside of the home	Never/Rarely	1227	32	81,370	1 (ref)	1 (ref)
	Occasionally	762	15	32,776	1.26 (0.63; 2.49)	1.24 (0.62; 2.48)
	Everyday/Most of the time	252	6	7731	2.55 (1.02; 6.35)	2.18 (0.81; 5.83)

CI confidence interval, DNC: model did not converge due too few events in one of the groups, HR hazard ratio, IPC infection prevention and control, ref reference, TSLI time since last infection, TSB time since booster dose

*adjusted for hospital only

**adjusted for age, sex, underlying conditions, hospital (as needed)

Factors associated with infection risk

Individual susceptibility factors

Age and sex did not present any statistically significant associations with SARS-CoV-2 infection in any period (Table 2 for pre-Omicron, Table 3 for pandemic Omicron, and Table 4 for post-pandemic Omicron). HCWs with underlying chronic conditions had a significantly higher infection risk during the post-pandemic Omicron period (aHR 1.39, 95% CI [1.06, 1.81], Table 4). A similar association was observed during pre-Omicron, but with wider confidence intervals (aHR 1.47, 95% CI [0.83, 2.63], Table 2).

Not receiving a COVID-19 booster vaccination in the previous 180 days suggested increased risk in some periods (aHR range 0.96–1.82), though with imprecise estimates Tables 2, 3 and 4). During the pandemic Omicron period, infection risk was higher among those never infected or last infected more than 12 months ago (aHR 1.37, 95% CI [1.10–1.70]), but this association disappeared in the post-pandemic Omicron period (aHR 1.0, 95% CI [0.66, 1.51]). During the pre-Omicron period, no PCR-confirmed infections were detected in previously infected individuals. Smoking and alcohol consumption presented with nonsignificant associations (Table S2).

Occupational risk factors

During the pre-Omicron period, ancillary workers had the highest risk of infection compared to medical doctors (aHR 3.86, 95% CI [1.30, 11.47]). Other roles showed elevated, but nonsignificant risks compared to medical doctors (aHR for allied professionals 1.56, 95% CI [0.45, 5.48], for administration/reception workers 1.99, 95% CI [0.71, 5.54], for nurses 1.23, 95% CI [0.52, 2.89]), and these associations decreased during the Omicron periods. Having a patient-facing occupation presented an aHR of 1.87 (95% CI [0.73, 4.83]) pre-Omicron, 0.88 (95% CI [0.69, 1.11]) during pandemic Omicron and 0.69 (95% CI [0.48, 1.00]) during the post-pandemic Omicron period.

Strict adherence to IPC and hand hygiene protocols were not associated with infection risk (Tables 2, 3 and 4 and Table S2). For example, the aHRs for always adequately wearing PPE (compared to not always) were 0.78 (95% CI [0.29, 2.07]), 0.92 (95% CI [0.70, 1.21]), and 1.33 (95% CI [0.87, 2.04]), for the three periods, respectively. Performing aerosol-generating procedures and workplace contact with COVID-19 cases were not significantly associated with infection (aHR range 0.88–1.15 with wide confidence intervals including 1).

Community risk factors

In the pre-Omicron period, household contact with a COVID-19 case at home increased the risk of infection four times (aHR 4.05, 95% CI [1.78, 9.19]), but this effect decreased over time (pandemic Omicron period 1.76, 95% CI [1.35, 2.31], post-pandemic Omicron period 1.30, 95% CI [0.83, 2.03], Tables 2, 3 and 4). Never or rarely wearing masks indoors significantly increased infection risk during the pandemic Omicron period (aHR 1.32, 95% CI [1.05, 1.65]).

Having frequent household visitors, maintaining physical distance indoors and using public transportation were not significantly associated with infection risk in any of the periods, although a trend towards higher infection rates were observed for having frequent household visitors in the pre-Omicron period. Attending social gatherings non-significantly decreased infection risk in the pre-Omicron period (aHR 0.63, 95% CI [0.22, 1.86]), however, it increased risk slightly, but not significantly, in the Omicron periods (aHR 1.15, 95% CI [0.91, 1.46] and 1.25, 95% CI [0.88, 1.78], respectively, all for the most frequent gathering category).

Using a single model with a period interaction instead of period-stratified models produced similar point estimates (< 10% difference) but wider confidence intervals (Figure S3). An exception was observed for immunity variables, where one association changed direction, likely due to sparse data and convergence issues arising from empty exposure–period cells in the pre-Omicron period. In another sensitivity analysis, adjusting for immunity variables had minimal impact on estimated HRs and corresponding 95% CIs (Figure S4).

Discussion

We evaluated risk factors for SARS-CoV-2 infection among HCWs using data from a European multicentre, hospital-based cohort, spanning different pandemic waves and the post-pandemic period. During the period

Table 3 Risk and protective factors of SARS-CoV-2 infection among HCWs in the pandemic Omicron period, VEBIS-HCW European multi-centre COVID-19 study, December 15, 2021– May 2, 2023. The number of included HCWs in each model as well as the events and person-time are listed for the crude models. These numbers can differ from the total number of included HCWs for each period either due to missing data in the assessed variable (lower number of included HCWs) or due to HCWs being included in multiple categories over the period for time-varying exposures

Exposure	Response	*N* HCWs	*N* events	Person-time	Crude* HR (95% CI)	Adjusted** HR (95% CI)
Sex	Female	1693	518	196,502	1 (ref)	1 (ref)
	Male	364	115	44,753	0.98 (0.8; 1.21)	0.97 (0.79; 1.2)
Age groups (years)	18–49	1406	430	157,093	1 (ref)	1 (ref)
	≥ 50	654	203	84,162	0.95 (0.8; 1.13)	0.96 (0.81; 1.14)
Any chronic condition	No	1486	448	169,197	1 (ref)	1 (ref)
	Yes	563	181	70,869	1.03 (0.86; 1.23)	1.04 (0.87; 1.24)
Time since last infection (TSLI)	TSLI 2–12 months	627	134	57,739	1 (ref)	1 (ref)
	> TSLI 12 months or never had an infection	1601	499	183,516	1.36 (1.1; 1.7)	1.37 (1.1; 1.7)
Time since last booster dose (TSB)	TSB 7–90 days	954	144	52,206	1 (ref)	1 (ref)
	TSB 91–180 days	848	133	48,116	1.42 (1.02; 1.96)	1.44 (1.04; 2)
	Never vaccinated or > TSB 180 days	1704	356	140,933	0.96 (0.75; 1.25)	0.96 (0.75; 1.25)
Occupational role	Medical Doctor	419	106	40,254	1 (ref)	1 (ref)
	Administration/Reception	254	90	33,425	1.1 (0.81; 1.48)	1.09 (0.8; 1.48)
	Allied professional	83	23	8314	1.19 (0.75; 1.9)	1.18 (0.74; 1.89)
	Ancillary	66	32	11,135	1.08 (0.7; 1.67)	1.09 (0.7; 1.68)
	Nurse/Nurse assistants	883	269	106,586	0.99 (0.78; 1.25)	0.98 (0.77; 1.24)
	Laboratory	117	48	14,547	1.23 (0.86; 1.75)	1.22 (0.86; 1.75)
	Other	219	60	24,835	1.02 (0.74; 1.41)	1.02 (0.73; 1.41)
Patient-facing occupation	No	230	96	32,381	1 (ref)	1 (ref)
	Yes	1677	499	192,322	0.88 (0.7; 1.12)	0.88 (0.69; 1.11)
Following IPC: Hand hygiene	Not always	108	24	11,387	1 (ref)	1 (ref)
	Always	865	228	88,362	1.08 (0.7; 1.67)	1.04 (0.67; 1.62)
Following IPC: Patient contact	Not always	128	33	12,910	1 (ref)	1 (ref)
	Always	828	213	83,343	0.93 (0.64; 1.37)	0.93 (0.64; 1.37)
Following IPC: Personal protective equipment	Not always	231	70	26,930	1 (ref)	1 (ref)
	Always	1049	299	116,729	0.92 (0.7; 1.21)	0.92 (0.7; 1.21)
Aerosol generating procedures	No	1736	497	190,949	1 (ref)	1 (ref)
	Yes	416	81	29,840	0.96 (0.75; 1.22)	0.95 (0.74; 1.21)
Contact with a case in the hospital	No	1286	363	137,479	1 (ref)	1 (ref)
	Yes	1046	224	86,817	0.95 (0.8; 1.13)	0.95 (0.8; 1.13)
Contact with a case at home	No	2006	563	223,842	1 (ref)	1 (ref)
	Yes	714	65	15,028	1.79 (1.37; 2.34)	1.76 (1.35; 2.31)
Frequency of taking public transit in the last week	Never	1452	313	126,322	1 (ref)	1 (ref)
	One to two times	967	94	38,629	0.95 (0.75; 1.21)	0.93 (0.73; 1.18)
	Three or more	1084	226	76,101	1.16 (0.97; 1.4)	1.16 (0.96; 1.39)
Masking indoors	Always/Often	1396	273	114,285	1 (ref)	1 (ref)
	Sometimes/Never/Rarely	1352	359	125,303	1.31 (1.05; 1.63)	1.32 (1.05; 1.65)
Attending gatherings	Never	1386	210	87,541	1 (ref)	1 (ref)
	One to two times	1626	299	109,521	1.11 (0.92; 1.33)	1.09 (0.91; 1.31)
	Three or more	969	124	43,580	1.17 (0.92; 1.48)	1.15 (0.91; 1.46)
Keeping distance indoors	Always/Often	1558	302	119,229	1 (ref)	1 (ref)
	Sometimes/Never/Rarely	1492	330	121,750	1.02 (0.87; 1.2)	1.03 (0.88; 1.21)

Table 3 (continued)

Exposure	Response	*N* HCWs	*N* events	Person-time	Crude* HR (95% CI)	Adjusted** HR (95% CI)
Having visitors from outside of the home	Never/Rarely	1870	478	183,112	1 (ref)	1 (ref)
	Occasionally	1046	121	43,421	1.08 (0.88; 1.32)	1.08 (0.88; 1.33)
	Everyday/Most of the time	335	34	14,524	0.94 (0.66; 1.35)	0.92 (0.64; 1.32)

CI confidence interval, DNC: model did not converge due too few events in one of the groups, HR hazard ratio, IPC infection prevention and control, ref reference, TSLI time since last infection, TSB time since booster dose

*adjusted for hospital only

**adjusted for age, sex, underlying conditions, hospital (as needed)

covered by our study, COVID-19 evolved from a global public health emergency to an endemic respiratory disease, with reduced severity due to widespread population immunity and vaccination. Over this period, societies largely returned to normal activities, while healthcare systems transitioned from emergency pandemic response to the routine management of COVID-19 alongside other respiratory infections [25, 26]. The main strength of our study is the prospective collection of community and occupational data with systematic follow-up and PCR testing, enabling the detection of mild or asymptomatic infections. Our findings highlight a temporal shift in risk factors, especially community risk factors which were important in the pre-Omicron period and declined in the subsequent time periods. In contrast, awareness of contact with SARS-CoV-2 in the workplace did not significantly increase infection risk, suggesting that IPC protocols in hospitals mitigated hospital-associated transmission.

Household SARS-CoV-2 exposure has been consistently reported as a major risk factor in previous studies [1, 5, 13], particularly after lifting strict contact restrictions in later pandemic periods. However, consistent with our findings, its influence seems to have diminished over time. This is likely because, as the study progressed, immunity among HCWs increased through vaccination and natural infections. It could also be partially explained by non-detection of cases, as testing rates outside of the study decreased over time. The emergence of the Omicron variant, which is characterised by increased transmissibility and immune evasion [15, 16], fundamentally altered infection dynamics. However, as the overall immunity in the population grew, the relative importance of different risk factors, including household exposure, likely shifted. Likewise, workplace exposure to SARS-CoV-2, which posed considerable risk among HCWs during early waves [1, 27], became less relevant in later waves [5], in line with our results.

The higher infection risk among ancillary workers and allied health professionals in the pre-Omicron period is consistent with findings from a systematic review that reported elevated risk in certain non-medical roles, such as cleaners [1]. However, evidence on patient-facing HCWs remains mixed: while some systematic reviews report an increased risk [1, 6], another study, spanning multiple waves, found no consistent differences by role [5]. Notably, this study also observed that other occupational risk factors (e.g. type of role, ward, and PPE-requiring tasks), were evident mainly during the second wave, when social distancing was enforced and vaccine coverage was low [5]. This aligns with our findings, which indicate that the risk associated with certain roles, such as ancillary personnel, which has been attributed to limited access to PPE [28], was highest in the pre-Omicron period but became non-significant thereafter. While clinical exposure was a major concern early in the pandemic, our results suggest that its relative importance as a risk factor diminished over time.

Although prior research demonstrates that adequate PPE and high IPC compliance reduce infection risk [6, 9, 12], we observed no clear association between strict adherence to PPE, IPC precautions and infection risk. This likely reflects a lack of variation in reported IPC adherence, as nearly all HCWs indicated always using PPE and following hand hygiene protocols. Social desirability bias, where HCWs may overreport compliance with safety measures, could also contribute to the absence of an observed effect [29, 30]. Moreover, unlike first-wave studies that linked inadequate PPE with increased risk, our analysis began in May 2021, when participating hospitals had sufficient PPE supplies. A recent meta-analysis spanning multiple waves confirmed that the protective effect of PPE was most evident during the first wave; later waves showed no clear association [1]. Non-pharmaceutical interventions like mask-wearing were still important in mitigating infection risks [1]. The association was not assessed in later periods due to changes in public health recommendations.

Similarly, our results on aerosol-generating procedures contrast with prior studies identifying these as occupational risk factors [2, 9, 10], but agree with other studies finding no significant association [13]. This discrepancy likely reflects differences in pandemic phase, PPE availability, and the low sample size in the pre-Omicron period. Regarding demographic characteristics, our findings align with previous research showing no clear association between age or sex and infection in HCWs [6, 11, 12].

Table 4 Risk and protective factors of SARS-CoV-2 infection among HCWs in the post-pandemic Omicron period, VEBIS-HCW European multi-centre COVID-19 study, September 1, 2024–April 30, 2024. The number of included HCWs in each model as well as the events and person-time are listed for the crude models. These numbers can differ from the total number of included HCWs for each period either due to missing data in the assessed variable (lower number of included HCWs) or due to HCWs being included in multiple categories over the period for time-varying exposures

Exposure	Response	*N* HCWs	*N* events	Person-time	Crude* HR (95% CI)	Adjusted** HR (95% CI)
Sex	Female	816	162	83,873	1 (ref)	1 (ref)
	Male	447	96	49,744	0.94 (0.72; 1.22)	0.91 (0.7; 1.18)
Age groups (years)	18–49	913	168	98,599	1 (ref)	1 (ref)
	≥ 50	348	89	34,729	1.37 (1.05; 1.78)	1.39 (1.06; 1.81)
Any chronic condition	No	205	26	14,104	1 (ref)	1 (ref)
	Yes	1116	232	119,513	0.99 (0.66; 1.49)	1 (0.66; 1.51)
Time since last infection (TSLI)	TSLI 2–12 months	188	24	11,503	1 (ref)	1 (ref)
	> TSLI 12 months or never had an infection	155	7	8710	1.47 (0.58; 3.74)	1.52 (0.6; 3.86)
Time since last booster dose (TSB)	TSB 7–90 days	1219	227	113,404	1.23 (0.79; 1.94)	1.22 (0.77; 1.91)
	TSB 91–180 days	222	34	22,459	1 (ref)	1 (ref)
	Never vaccinated or > TSB 180 days	179	44	19,569	1.3 (0.81; 2.07)	1.26 (0.78; 2.02)
Occupational role	Medical Doctor	34	8	3437	1.35 (0.6; 3.03)	1.27 (0.56; 2.87)
	Administration/Reception	50	9	6531	0.59 (0.28; 1.27)	0.59 (0.27; 1.27)
	Allied professional	578	122	61,836	1.11 (0.75; 1.65)	1.05 (0.7; 1.58)
	Ancillary	58	14	5254	1.33 (0.7; 2.52)	1.27 (0.66; 2.42)
	Nurse/Nurse assistants	130	27	14,020	1.23 (0.73; 2.07)	1.22 (0.73; 2.05)
	Laboratory	129	36	12,097	1 (ref)	1 (ref)
	Other	1116	220	119,431	0.71 (0.49; 1.02)	0.69 (0.48; 1)
Patient-facing occupation	No	97	16	8708	1 (ref)	1 (ref)
	Yes	691	138	73,276	0.94 (0.55; 1.61)	0.93 (0.54; 1.6)
Following IPC: Hand hygiene	Not always	127	18	11,581	1 (ref)	1 (ref)
	Always	663	137	70,484	1.19 (0.71; 1.99)	1.17 (0.7; 1.97)
Following IPC: Patient contact	Not always	206	32	20,810	1 (ref)	1 (ref)
	Always	592	123	61,677	1.35 (0.88; 2.06)	1.33 (0.87; 2.04)
Following IPC: Personal protective equipment	Not always	1194	225	119,516	1 (ref)	1 (ref)
	Always	229	31	12,933	1.2 (0.81; 1.76)	1.15 (0.78; 1.71)
Aerosol generating procedures	No	851	140	78,939	1 (ref)	1 (ref)
	Yes	739	117	53,813	0.98 (0.75; 1.28)	0.98 (0.75; 1.28)
Contact with a case in the hospital	No	1197	228	123,420	1 (ref)	1 (ref)
	Yes	332	23	6794	1.32 (0.85; 2.06)	1.3 (0.83; 2.03)
Contact with a case at home	No	741	88	55,241	1 (ref)	1 (ref)
	Yes	619	57	23,584	1.37 (0.97; 1.95)	1.37 (0.97; 1.94)
Frequency of taking public transit in the last week	Never	798	112	54,426	1.21 (0.9; 1.64)	1.21 (0.9; 1.64)
	One to two times	818	79	43,201	1 (ref)	1 (ref)
	Three or more	987	106	56,311	1.07 (0.79; 1.45)	1.07 (0.79; 1.45)
Attending gatherings	Never	676	72	33,739	1.25 (0.88; 1.78)	1.25 (0.88; 1.78)
	One to two times	816	162	83,873	1 (ref)	1 (ref)
	Three or more	447	96	49,744	0.94 (0.72; 1.22)	0.91 (0.7; 1.18)

CI confidence interval, DNC: model did not converge due too few events in one of the groups, HR hazard ratio, IPC infection prevention and control, ref reference, TSLI time since last infection, TSB time since booster dose

*adjusted for hospital only

**adjusted for age, sex, underlying conditions, hospital (as needed)

Several limitations of the study warrant consideration. First, the dynamic participation throughout the study period, according to the ethical approval timing and local requirements for active surveillance for SARS-CoV-2 infections may have reduced comparability across participants per period. Secondly, small sample sizes in some exposure categories reduced statistical power, particularly in the pre-Omicron period, necessitating broad

variable groupings (e.g., combining IPC adherence into "always" vs. "not always"). Sparse events also prevented analysis of specific workplace settings such as hospital ward type. Thirdly, the exposures were self-reported and may therefore be subject to misclassification, particularly through social desirability bias (e.g., overreporting adherence to protective behaviours). Poor recall or recall bias is unlikely, as exposures were assessed prospectively at enrolment and weekly thereafter. However, IPC variables were only collected at the start of each period, which may have led to misclassification and probable bias toward the null if behaviours changed during follow-up. The absence of any effects of IPC variables should therefore be interpreted with caution. Finally, our classification of pre-Omicron versus Omicron periods used a single cutoff date, which was established based on the data available at the study level, and not at the country level from reports in GISAID. Limited sample size precluded further stratification by Omicron sublineages.

In conclusion, HCWs remain a priority group for prevention of infections with SARS-CoV-2 and other respiratory pathogens. Our results illustrate how infection risk factors evolved as the pathogen evolved and behaviours changed, with community exposures playing a more important role during the pandemic phase of the study and the occupational exposures being less prominent in later stages of the pandemic, as IPC measures, PPE availability, and host immunity through previous infections and vaccinations improved. Nonetheless, differences across occupational roles suggest that prevention efforts should extend beyond clinical staff to include ancillary, allied, and administrative personnel. The observed contribution of community and household exposures to SARS-CoV-2 infection risk among HCWs during the pandemic demonstrates that infection prevention strategies cannot focus exclusively on workplace exposures. Protecting HCWs therefore requires a more comprehensive approach that combines occupational infection prevention and control measures with interventions extending beyond the healthcare setting, including timely vaccination and screening strategies in all health personnel, not only in the clinical staff. Integrating these measures into long-term occupational health policies can reduce the risk of respiratory infections among HCWs, strengthen workforce protection, maintain healthcare system resilience, and improve preparedness for future public health emergencies.

Abbreviations

aHR	Adjusted Hazard Ratio
CI	Confidence Interval
COVID-19	Coronavirus Disease 2019
DNC	Did not converge
ECDC	European Centre for Prevention and Control
HCW	Healthcare Worker
HR	Hazard Ratio
IPC	Infection Prevention and Control
PT	Person-time
PCR	Polymerase Chain Reaction
PPE	Personal Protective Equipment
RT-PCR	Reverse Transcription Polymerase Chain Reaction
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
TSB	Time since booster dose
TSLI	Time since last infection
VEBIS	Vaccine Effectiveness, Burden, and Impact Studies

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12879-026-14127-3.

Supplementary Material 1

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Author contributions
I.G contributed to the statistical plan of analysis, conducted the analysis, interpreted and reviewed results, and wrote the manuscript. M.R.C supported the coordination of the VEBIS HCWs network and study design, led the statistical plan of analysis, contributed to data cleaning, and reviewed the manuscript. K.B and S.B were involved in the study design, interpretation of results, and reviewing the manuscript. C.S coordinates the VEBIS HCWs network, was involved in the study's original methodological design (generic protocol), supported the statistical plan of analysis, reviewed and interpreted results, and reviewed the manuscript. A.N supported the coordination of the VEBIS HCWs network, was involved in the study's original methodological design (generic protocol), reviewed and interpreted results, and reviewed the manuscript. Z.L.M, A.U, C.B, C.F, P.B, R.M, V.Z, D.Z, K.S, V.G, C.P.P, M.C, R.M.H, M.C.P, M.L.M, G.P, L.L, J.M, A.S, K.G.D, I.A, D.G, A.M, S.A.F, M.L, P.S.C, L.C, G.S, J.S, C.K, R.S, D.K, E.A.B, C.V.H, A.G.K, S.M.P, V.D.M, C.M.A, A.M.M and the VEBIS HCW VE study group were responsible for the coordination of the study at the national/regional/hospital level, contributed to developing the study site-specific protocols, were in charge of the collection, management and validation of the clinical and laboratory data. They interpreted the results, reviewed and contributed to all manuscript versions. All authors read and approved the final manuscript.

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Data availability
The data used in this study can be obtained upon reasonable request to the corresponding author.

Declarations

Ethics approval and consent to participate
Written informed consent to participate was obtained from all study participants prior to enrolment, in accordance with the Declaration of Helsinki. The study was approved by the Ethical review committees of each participating hospital: Ethics Committee of the Croatian Institute of Public Health (HZJZ) Croatia, Zagreb: 381-15-21-3; University of Tartu Human Research Ethics Committee, Estonia: 382/M-7; Clinical research ethics committee, Galway University Hospital, Ireland: C.A. 2693; SJH/TUH Joint Research Ethics Committee, Ireland: 0513; Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Department of Security and Bioethics, Rome, Italy: 00372/23; Università degli Studi di Milano-Bicocca presented same approval as Policlinico Gemelli, Università Cattolica del Sacro Cuore, Rome, Italy; Ethics Committee for Clinical Research at Pauls Stradins Clinical University Hospital, Latvia: 241023–3L; Ethics Committee for Clinical Research at Pauls Stradins Clinical University Hospital, extended to Children Clinical University Hospital, Latvia: 241023–10L; Ethics and Supervision Committee for Research on Humans and Animals at the Central Clinical Hospital of the Ministry of Internal Affairs and Administration in Warsaw, Poland, Warszawie: 15/2022; Ethics Committee of the Clinical Hospital for Infectious and Tropical Diseases "Dr. Victor Babes", Romania: 14420; Local Ethics Commission of the Central Military Emergency University Hospital "Carol Davila", Romania: 646, Approval Date: 7 November 2023; Research-Development Ethics Committee of the National Institute for Maternal and Child Health "Alessandrescu-Rusescu", Approval Code: 1464, Approval Date: 18 January 2023; Research Ethics Committee of the Autonomous Community of Aragon (CEICA), HU Miguel Servet, Zaragoza, Spain: PI21-176 and PI22/483; Ethics Committee for Research with Medicines, Sant Joan de Déu, Research Foundation, Barcelona, Spain: 17/2023.

Competing interests
C.P.P and S.A.F reported speaker fees from and participation in the advisory boards of Pfizer and MSD. S.A.F reports also participating in the Advisory Board of Gilead. C.M.A reported speaker fees from MSD, Pfizer and Sanofi. J.S reported support for attending the ESID conference 2022 from Takeda Pharmaceutical. R.M.H and S.M.P reported a grant attributed to their institution on "PSCD Longitudinal evaluation of SARS-CoV-2 immune status post-natural infection and post-vaccination". S.M.P also reported payments for presentations from and travel support from Gilead, MSD, and the Society of Infectious Diseases and HIV/AIDS, Romania. All other authors declare no conflicts of interest related to this work.

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