BMC Medicine

RESEARCH

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Hybrid, infection- and vaccination-induced protection against laboratory- confirmed SARS-CoV-2 infection in a European multi-centre prospective cohort of healthcare workers, 2021–2024

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Abstract

Background Healthcare workers (HCWs) face high occupational exposure to SARS-CoV-2 and are a priority group for vaccination. Both natural infection and vaccination—individually or combined as hybrid immunity—confer protection against SARS-CoV-2 infection. This study aimed to evaluate the protection conferred by hybrid, infection-induced, and booster vaccine-induced immunity against laboratory-confirmed SARS-CoV-2 infections in HCWs during the circulation of three pandemic and one post-pandemic Omicron sublineages.

Methods We conducted a prospective cohort study of HCWs from 18 hospitals across nine European countries. Participants underwent RT-PCR testing at enrolment and during weekly or fortnightly follow-ups. The study period was divided based on dominant Omicron sublineage circulation: BA.1/2 (Dec 16, 2021–Jun 1, 2022), BA.4/5/BQ.1 (Jun 2–Dec 31, 2022), BA.2/XBB (Jan 1–May 2, 2023), and post-pandemic XBB.1.5/BA.2.86 (Sep 1, 2023–May 21, 2024). Participants were classified into four groups: hybrid (prior infection and recent booster vaccination 7–179 days), infection-induced (prior infection, no recent vaccination), vaccine-induced immunity (recent booster vaccination, no prior

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infection), and a reference group (no prior infection, no recent booster vaccination). Adjusted hazard ratios (aHRs) for infection were estimated using Cox regression, adjusting for hospital, age, sex, chronic condition, and patient-facing role.

Results A total of 3 133 HCWs were included: 2572 (82%) female, 1734 (55%) aged 40–59, and 563 (29%) with ≥ 1 chronic condition. Hybrid immunity showed significant protection during BA.1/2 (aHR = 0.37, 95%CI 0.21–0.63), BA.4/5/BQ.1 (aHR = 0.36, 95%CI 0.22–0.58), and XBB.1.5/BA.2.86 (aHR = 0.53, 95%CI 0.37–0.74) periods. Infection-induced immunity was protective across all periods, most during BA.1/2 (aHR = 0.26, 95%CI 0.12–0.53), and least during BA.2/XBB (aHR = 0.66, 95%CI 0.36–1.22). Vaccine-induced immunity alone offered limited protection during BA.1/2 (aHR = 0.72, 95%CI 0.49–1.06) and BA.4/5/BQ.1 (aHR = 0.77, 95%CI 0.50–1.19), with wide confidence intervals suggesting low statistical significance.

Conclusions Hybrid and infection-induced immunity groups were more protected against infection caused by earlier Omicron sub-lineages and more protected than vaccination alone, which had no significant protective effect. These findings highlight the need for adaptive public health strategies, including timely vaccine updates and understanding of prior SARS-CoV-2 infection to inform COVID-19 vaccination policies for HCWs in the post-pandemic era.

Keywords Hybrid immunity, Healthcare workers, Prospective cohort study, COVID-19 vaccination, Omicron variant

Background

Vaccination against the coronavirus disease 2019 (COVID-19) and natural infection caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can each induce immunological protection against SARS-CoV-2 infection. The combined protection is known as hybrid immunity. High incidence of SARS-CoV-2 infections alongside vaccination efforts has led to a substantial proportion of the population acquiring hybrid immunity at different times during pandemic and post-pandemic waves [1, 2].

Healthcare workers (HCWs) have been prioritised for COVID-19 vaccination in most past COVID-19 vaccination campaigns in Europe, including during the post-pandemic era. Targeting HCWs aimed at reducing disease burden due to their heightened risk of occupational exposure, safeguard essential services, and prevent onward transmission to patients who may be at higher risk of severe COVID-19 outcomes [3–7].

In the initial phase after COVID-19 vaccine introduction, primary course vaccination campaigns utilised vaccines that had been developed against the original SARS-CoV-2 virus. Although these vaccines offered high and long-lasting protection against severe disease [8], their protection against infection was good but short-lived [3, 4], which was reduced by the emergence of new variants [4, 5]. In the context of limited vaccine supply in 2021, several European countries adopted single-dose and extended-interval strategies for individuals with recent prior SARS-CoV-2 infection(s), supported by evidence that hybrid immunity offered robust protection [4]. With the emergence of the Omicron variant in late 2021, COVID-19 booster doses were mainly recommended regardless of prior SARS-CoV-2 infections [5], first using the original vaccines, and later the updated formulations [6]. In European Union (EU) member states, a first booster dose was recommended in the latter half of 2021, and a second booster dose for high-risk groups, including HCWs, in the spring of 2022 [6]. During the autumn 2022 campaign, the vaccination strategy shifted from regular booster doses to seasonal vaccination of prioritised vulnerable and high-risk groups regardless of the number of previous doses [6]. After advice from the European Medicines Agency (EMA), the European Commission authorised the bivalent mRNA COVID-19 vaccines containing the original and the Omicron BA.1 or BA.4/5 strains in August–September 2022. These were then rolled out throughout the autumn 2022 campaign [7]. During the autumn 2023 vaccination campaign in the EU and after WHO ended the COVID-19 as a Public Health Emergency of International Concern (PHEIC) on May 5, 2023 [9], the monovalent Omicron XBB.1.5 vaccine became available [10], and several countries reimplemented extended-interval strategies for individuals with recent prior SARS-CoV-2 infections [6].

Real-world evidence on infection-induced and hybrid immunity, especially in the post-pandemic era, remains limited [11–14], particularly among HCWs during Omicron waves (characterised by high transmissibility and lower severity). Understanding the evolution of hybrid, infection- and booster vaccination-induced protection is crucial for further developing COVID-19 vaccination policies. Within the framework of the Vaccine Effectiveness Burden and Impact Studies (VEBIS) project [15], we measured the effect of hybrid, infection or vaccine-induced immunity against SARS-CoV-2 infection during

BA.1/2, BA.4/5/BQ.1, BA.2/XBB, and XBB.1.5/BA.2.86 Omicron sub-lineage predominant circulation periods, among HCWs from a cohort study who had completed the primary vaccination course.

Methods

This study was embedded in the multi-centre dynamic prospective cohort among HCWs recruited from 18 hospitals in nine European countries (Croatia, Estonia, Ireland, Italy, Latvia, Poland, Portugal, Romania, and Spain). All HCWs from study hospitals were invited to participate, irrespective of their job role [15]. Hospitals participated according to their availability, and HCWs committed to a minimum 3-month follow-up (Additional file 1: Figure S1). In this analysis, we included HCWs who participated during the predominant circulation of Omicron sub-lineages: from 16 December 2021 to 2 May 2023 (pandemic Omicron period characterised by the predominant circulation of BA.1/2, BA.4/5/BQ.1, BA.2/XBB sublineages) and from 1 September 2023 to 21 May 2024 (post-pandemic Omicron period, characterised by the predominant circulation of XBB1.5/BA.2.86 sublineages) (Additional file 1: Figure S1).

Study procedures

HCW completed a questionnaire at enrolment, gathering information on demography, clinical history (including vaccination history, prior SARS-CoV-2 infection) and occupational and community behaviour. Weekly follow-up questionnaires gathered updates on vaccination status, possible professional and personal exposures to SARS-CoV-2 and if diagnosed with SARS-CoV-2 infection outside of the study. Vaccination information was validated using available data sources at the site level: electronic records, vaccination registries, occupational health registries, vaccination certificates.

Participants provided specimens for reverse transcription polymerase chain reaction (RT-PCR) testing at enrolment and follow-up through either weekly saliva ($n=4$ sites) or weekly ($n=8$ sites) or fortnightly ($n=6$ sites) naso- and/or oropharyngeal specimens (according to the procedures at the site level), to ascertain cases of SARS-CoV-2 infection. Confirmatory RT-PCR testing was also conducted when participants (1) reported a positive SARS-CoV-2 test outside of the study (initially reported as RT-PCR test, antigen detection rapid diagnostic test [AgRDT], Computerised Tomography scan [CT scan] or self-reported diagnostic), (2) reported COVID-19 compatible symptoms, or (3) reported close contact with an individual who tested positive for SARS-CoV-2 in the previous 14 days. Participating HCWs also provided blood samples for serology testing, antibodies to the nucleocapsid protein [anti-N] and spike protein [anti-S].

Exclusion criteria

HCWs who did not respond to an enrolment or any regular follow-up questionnaires, and those with missing or incompatible information on age, sex, or vaccination status, were excluded from analyses (Additional file 1: Figure S2). In this analysis, we also excluded the following participants: (1) immunocompromised individuals due to specific recommendations on primary course vaccination, (2) those with serologic evidence of infection during the study (in 4 sites) not concordant with the virology testing (i.e., positive anti-N following a negative anti-N test, in the absence of a positive RT-PCR test), (3) those not contributing to person-time in an analysis period, (4) those with missing information on prior infection (status and/or date) at enrolment, (5) those with person-time contribution of less than 60 days after a SARS-CoV-2 prior infection, and (6) those unvaccinated or partially vaccinated (we considered that these HCWs represent a specific population with potentially different demographic, professional, or behavioural characteristics).

Exposures and outcome definitions

We defined the following exposure groups: (1) hybrid immunity (+/+) HCWs that reported at least one prior SARS-CoV-2 infection ($\geq$60 days) and recent (7–179 days) booster vaccination regardless of whether the infection occurred before or after vaccination, and the number of doses of vaccine received; (2) infection-induced immunity (+/−): prior infection with waned vaccination ($\geq$180 days); (3) vaccination-induced immunity (−/+) of no prior infection with recent (7–179 days) vaccination; and the reference group (−/−) of no prior infection and waned vaccination ($\geq$180 days). We assumed HCWs vaccinated $\geq$180 days ago as no longer exhibiting vaccine-induced immunity ("waned vaccination") [8].

HCWs were considered as having completed booster vaccination if $\geq$7 days had elapsed from receipt from the first or the second booster dose. We discarded person-time immediately after vaccination (0–6 days following booster uptake).

We defined a SARS-CoV-2 reinfection as an infection occurring at least 60 days after a preceding infection. We discarded person-time immediately after infection (0–60 days post-symptom-onset and/or the swab date of a positive test if no symptoms were reported) [16]. Prior infection status was ascertained at the beginning of the person-time contribution for each analysis period. The sources of information considered were as follows: (1)

Pre-enrolment infections documented in the enrolment or re-enrolment questionnaires (self-reported and validated by clinical monitors where possible), (2) RT-PCR confirmed infection detected within the study but before the start of the analysis period, (3) RT-PCR confirmed infection detected outside the study and documented in the follow-up questionnaires before the start of the analysis period. The prior infection status was updated when a participant re-entered the study following an infection.

For all analyses, the primary outcome was RT-PCR-confirmed SARS-CoV-2 infection or re-infection regardless of symptoms.

Sub-lineage predominance analysis periods

We defined the predominant SARS-CoV-2 sub-lineage periods (≥75%) by comparing the percentage over time for each circulating sub-lineage across participating countries, using national data reported to the European Respiratory Virus Surveillance Summary (ERVISS) [17]. We grouped time consecutive Omicron sublineages following an operational clustering approach based on lineage relationships, and epidemiological importance. We defined the following periods during the pandemic period: Omicron BA.1/2 from 16 December 2021 to 1 June 2022 (first Omicron wave), Omicron BA.4/5/BQ.1 from 2 June 2022 to 31 December 2022 (variants descendants of the same branch, causing the second Omicron wave), and Omicron BA.2/XBB from 1 January 2023 to 2 May 2023 (XBB—derived from BA.2, causing the third Omicron wave). The second analysis period included post-pandemic Omicron XBB.1.5/BA.2.86 (comprising JN.1) from 1 September 2023 to 21 May 2024 (Additional file 1: Figure S3). We defined this period as post-pandemic, marking the end of COVID-19 as a PHEIC and the start of seasonal evaluation of vaccine effectiveness.

Statistical analysis

We used Cox proportional hazards models to estimate hazard ratios (HR) for each exposure group compared to the reference group defined above. We classified HCWs in time-varying exposure groups according to changes in vaccination status and prior infection. Consequently, a single participant may have contributed person-time to multiple exposure categories.

Cox regression was performed using study time as the time scale and a complete case approach. We used the Schoenfeld residual test to check the proportional hazards assumption. We calculated unadjusted and adjusted HR (aHR), including hospital as a stratification factor to account for site-specific variation. We adjusted the multivariable regression model using a priori chosen covariates: age, sex, presence of at least one underlying chronic condition (yes/no) and whether the participant's occupational role was patient-facing (yes/no). The decision to include age categories or splines, and the number of knots, was based on the Akaike Information Criterion.

Multiple comparisons between treatment levels were performed using Tukey's method. Adjusted *p*-values and confidence intervals were reported for pairwise contrasts [18].

Person-time contribution began at the later of the start of each sub-lineage circulation period or the participant's enrolment date. Follow-up was censored at the earliest of: (1) RT-PCR confirmed SARS-CoV-2 infection (primary outcome), (2) loss to follow-up (as reported or as defined below), or (3) the end of the Omicron circulation period (as defined above). Exposure groups were reclassified according to changes in prior infection and vaccination over time.

We excluded person-time during the gaps in virology testing (28 days between two tests if any follow-up questionnaire was completed, or 42 days if at least one questionnaire was completed). If the participant did not undergo virological testing after this elapsed time, we considered them as lost to follow-up.

All analyses were conducted using R version 4.1.3, the models and multiple comparisons were implemented using the "survival" and "multcomp" packages.

This observational study was conducted and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (Additional file 2).

Results

The cohort counted 4431 HCWs from nine countries; 3327 HCWs participated in the pandemic Omicron period, and 1477 in the post-pandemic Omicron period. After applying exclusion criteria (Additional file 1: Figure S2), 3133 (70%) HCWs contributed person-time to the analysis in at least one Omicron sub-lineage predominant period: 1603 HCWs during BA.1/2, 1526 during BA.4/5/BQ.1, 1026 during BA.2/XBB, and 1131 during XBB.1.5/BA.2.86. The median follow-up time was 152 days (Interquartile range [IQR 79–204]), with 7% of HCWs lost to follow-up over the entire period.

Among the 3133 HCWs included in the analysis, 2572 (82%) were female, 1734 (55%) aged 40–59 years, 567 (18%) reported one or more chronic conditions, and 2266 (72%) engaged in patient-facing interaction with 2087 (67%) in a clinical role as nurses and medical doctors. Demographic characteristics of HCWs were generally comparable across the different analysis periods, except for fewer HCWs with patient-facing roles participating during Omicron BA.2/

Table 1 Demographic characteristics of participant HWC at the start of each Omicron sub-lineage predominant circulation period, multi-centre VEBIS HCW COVID-19 vaccine effectiveness study, 16 Dec 2021–21 May 2024

	Omicron BA.1/2	Omicron BA.4/5/BQ.1	Omicron BA.2/XBB	Omicron XBB.1.5/ BA.2.86
	N = 1 603	*N* = 1 526	*N* = 1 026	*N* = 1 131
Age groups				
18–39	548 (34%)	497 (33%)	346 (34%)	366 (32%)
40–59	900 (56%)	879 (58%)	591 (58%)	668 (59%)
≥60	155 (10%)	150 (10%)	89 (9%)	97 (9%)
Sex				
Female	1293 (81%)	1249 (82%)	882 (86%)	944 (83%)
Male	310 (19%)	277 (18%)	144 (14%)	187 (17%)
Occupation				
Medical Doctors	302 (19%)	256 (17%)	199 (19%)	189 (17%)
Nurses/nurse assistants	808 (50%)	723 (47%)	418 (41%)	488 (43%)
Laboratory	89 (6%)	95 (6%)	41 (4%)	57 (5%)
Administration/Reception	171 (11%)	196 (13%)	173 (17%)	172 (15%)
Ancillary	36 (2%)	37 (2%)	37 (4%)	45 (4%)
Other	197 (12%)	219 (14%)	158 (15%)	180 (16%)
Facing Patients				
Yes	1197 (75%)	1076 (71%)	700 (68%)	751 (66%)
No	406 (25%)	450 (29%)	326 (32%)	380 (34%)
Number of chronic conditions				
One	199 (12%)	200 (13%)	141 (14%)	130 (11%)
Two or more	93 (6%)	97 (6%)	71 (7%)	69 (6%)
None	1311 (82%)	1229 (81%)	814 (79%)	932 (82%)

Participants were characterised at the onset of their person-time contribution to each analysis period

Countries contributing to BA.1/2 (EE, ES, HR, IE, IT, LV, PT), BA.4/5/BQ.1 (EE, ES, HR, IE, LV, PL, PT), BA.2/XBB (EE, IE, LV, PT, RO, ES), XBB1.5/BA.2.86 (EE, IE, IT, LV, PT, RO, ES) Omicron sub-lineage predominant circulation periods

COVID-19 coronavirus disease 2019, *HCWs* Healthcare workers, *VEBIS* Vaccine Effectiveness Burden and Impact Studies

XBB and XBB.1.5/BA.2.86 periods, compared with Omicron BA.1/2 (p-value 0.001) (Table 1).

Description of prior SARS-CoV-2 infection and booster vaccination during the Omicron sub-lineage predominant circulation periods

Throughout all Omicron periods, the proportion of HCWs in the hybrid immunity exposure group ranged from 14 to 29%. The highest proportion was observed at the beginning of the BA.2/XBB period. The proportion of HCWs in the infection-induced immunity exposure group increased from 12% at the beginning of the BA.1/2 period to 74% at the beginning of the XBB.1.5/BA.2.86 period. Conversely, the proportion of HCWs with vaccination-induced immunity exposure group decreased from 59 to 2% over the same periods (Table 2). Among HCWs with information on the timing of previous infection, the proportion of HCWs with a recent prior infection (60–180 days) also decreased, from 54% at the start of the BA.4/5/BQ.1 period to 18% at the start of the XBB.1.5/BA.2.86 period.

Among individuals with recent vaccination, the time since the last booster vaccination was longer during the BA.4/5/BQ.1 period (median 166 days; range 7–179) and shorter during the BA.2/XBB period (median 77 days; range 7–176). Time since booster vaccination was similar among those with and without prior infection (data not shown).

The time since the last infection was shorter during the BA.4/5/BQ.1 period (median 204 days; range 60–999) and longer during the XBB.1.5/BA.2.86 period (median 542 days; range 60–1371) (Table 2).

Among those with waned vaccination, the time since last vaccination was shortest during BA.4/5/BQ.1 (median 222 days; range 180–698) and longest during XBB.1.5/BA.2.86 (median 700 days; range 213–1095). Similarly, the time since prior infection was shorter during BA.1/2 (median 312 days; range 60–1453) and longer during XBB.1.5/BA.2.86 (median 477 days; range

Table 2 Description of exposure groups at the start of each Omicron sub-lineage predominant circulation period, multi-centre VEBIS HCW COVID-19 vaccine effectiveness study, 16 Dec 2021–21 May 2024

	Omicron BA.1/2	Omicron BA.4/5/BQ.1	Omicron BA.2/XBB	Omicron XBB.1.5/BA.2.86
Exposure	*N* = 1603	*N* = 1526	*N* = 1206	*N* = 1131
(+/+) Hybrid immunity	271 (17%)	240 (16%)	296 (29%)	158 (14%)
(+/–) Infection-induced immunity	186 (12%)	640 (42%)	530 (52%)	834 (74%)
(–/+) Vaccination-induced immunity	949 (59%)	201 (13%)	86 (8%)	23 (2%)
(–/–) No prior infection and waned vaccination	197 (12%)	445 (29%)	114 (11%)	116 (10%)
Recent prior SARS-CoV-2 infection	*N* = 457	*N* = 880	*N* = 826	*N* = 950
Yes (60–180 days)	216 (47%)	474 (54%)	191 (23%)	173 (18%)
No (> 180 days)	225 (49%)	329 (37%)	565 (68%)	776 (82%)
Missing	16 (4%)	77 (9%)	70 (8%)	1 (0%)
Time since last booster vaccination (7–179 days)	*N* = 1220	*N* = 441	*N* = 382	*N* = 139
Days (median, range)	36 (7–179)	166 (7–179)	77 (7–176)	35 (7–172)
Time since last booster vaccination (≥ 180 days)	*N* = 383	*N* = 1085	*N* = 644	*N* = 950
Days (median, range)	294 (180–484)	222 (180–698)	427 (182–811)	700 (213–1095)
Time since last prior SARS-CoV-2 infection (recent vaccination 7–179 days)	*N* = 271	*N* = 240	*N* = 296	*N* = 158
Days (median, range)	347 (60–817)	204 (60–999)	294 (60–1050)	542 (60–1371)
Time since last prior SARS-CoV-2 infection (waned vaccination ≥ 180 days)	*N* = 186	*N* = 640	*N* = 530	*N* = 834
Days (median, range)	112 (60–799)	140 (60–905)	262 (60–1134)	477 (60–1453)

COVID-19 coronavirus disease 2019, *HCWs* healthcare workers, *SARS-CoV-2* Severe Acute Respiratory Syndrome Coronavirus 2, *VEBIS* Vaccine Effectiveness Burden and Impact Studies

60–1453) (Table 2). Time since vaccination booster was similar among those with and without prior infection (data not show).

Additionally, at the start of the BA.1/2 period, 94% of individuals with recent vaccination had received their first booster dose as their last dose, and 76% had received the Comirnaty monovalent original (Pfizer/BioNTech) vaccine. By contrast, at the start of the XBB.1.5/BA.2.86 period, 63% had received a third booster dose as their last dose, and 83% had been vaccinated with the Comirnaty Omicron XBB1.5 adapted monovalent (Pfizer/BioNTech) vaccine (Additional file 3: Table S1).

During the study period, the percentage of asymptomatic prior infection ranged from 1 to 15% and the number of HCWs reporting multiple infections increased from 12 to 30% (2 infections) and from 0 to 12% (3 infections or more) (Additional file 3: Table S1).

Description of SARS-CoV-2 infections

Throughout the different pandemic and post-pandemic periods, 959 PCR-confirmed SARS-CoV-2 infections were detected, of which 570 (59%) were symptomatic, and 919 (96%) were identified through the study. No infection events detected within the study and included in this analysis required hospitalisation due to COVID-19. Among HCWs with information available, 377/897 (42%) reported a contact with a COVID-19 case, 286 (76%) contact in the hospital within the previous 14 days, 41 (11%) in the community, and 50 (13%) in both. Of all infections, 315 (33%) occurred during BA.1/2, 305 (32%) during BA.4/5/BQ.1, 122 (13%) during BA.2/XBB, and 217 (23%) during XBB1.5/BA.2.86 Omicron sub-lineage predominant circulation periods. Of all HCWs infected, 56 (7%) had multiple infections during the study period.

Hybrid, infection-, and vaccination-induced immunity

During the BA.1/2 and BA.4/5/BQ1 Omicron sub-lineage periods, the aHRs of infection in the hybrid immunity exposure group were 0.37 (95% confidence interval [CI] 0.21–0.63) and 0.36 (95%CI 0.22–0.58), respectively. Among HCWs from the infection-induced immunity exposure group, the aHR was 0.26 (95%CI 0.12–0.53) during BA.1/2 and 0.45 (95%CI 0.34–0.59) during BA.4/5/BQ.1. In the vaccine-induced immunity exposure group, the aHRs were 0.72 (95%CI 0.49–1.06) and 0.77 (95%CI 0.50–1.19) for the same periods (Table 3, Fig. 1).

During the BA.2/XBB Omicron pandemic period, the aHR of infection in the hybrid immunity exposure group was 0.91 (95%CI 0.45–1.85), while in the infection-induced immunity exposure group was 0.66 (95%CI 0.36–1.22). In addition, the aHR of the vaccine-induced immunity exposure group was aHR of 2.05 (95%CI 0.96–4.40) (Table 3, Fig. 1).

Table 3 Hybrid, prior SARS-CoV-2 infection and COVID-19 vaccination protection against PCR-confirmed SARS-CoV-2 infection during the Omicron sub-lineage predominant circulation, multi-centre VEBIS HCW COVID-19 vaccine effectiveness study, 16 Dec 2021–21 May 2024

	Person-days	Events	HR	HR (95% CI)	aHR	aHR (95% CI)
Omicron BA.1/2						
(–/–) No prior infection and waned vaccination	11,848	42	Ref	Ref	Ref	Ref
(+/+) Hybrid immunity	24,137	38	0.38	0.22–0.65	0.37	0.21–0.63
(+/–) Infection-induced immunity	12,145	10	0.27	0.13–0.55	0.26	0.12–0.53
(–/+) Vaccination-induced immunity	76,135	225	0.73	0.50–1.08	0.72	0.49–1.06
Omicron BA.4/5/BQ.1						
(–/–) No prior infection and waned vaccination	32,913	120	Ref	Ref	Ref	Ref
(+/+) Hybrid immunity	16,758	25	0.36	0.22–0.59	0.36	0.22–0.58
(+/–) Infection-induced immunity	73,957	131	0.46	0.35–0.60	0.45	0.34–0.59
(–/+) Vaccination-induced immunity	8741	29	0.78	0.50–1.22	0.77	0.50–1.19
Omicron BA.2/XBB						
(–/–) No prior infection and waned vaccination	7670	19	Ref	Ref	Ref	Ref
(+/+) Hybrid immunity	21,895	31	0.96	0.50–1.86	0.91	0.45–1.85
(+/–) Infection-induced immunity	39,738	54	0.69	0.39–1.24	0.66	0.36–1.22
(–/+) Vaccination-induced immunity	6522	18	1.96	0.91–4.23	2.05	0.96–4.40
Omicron XBB.1.5/BA.2.86						
(–/–) No prior infection and waned vaccination	13,564	40	Ref	Ref	Ref	Ref
(+/+) Hybrid immunity	23,474	25	0.51	0.30–0.87	0.51	0.30–0.87
(+/–) Infection-induced immunity	92,006	143	0.54	0.38–0.76	0.53	0.37–0.74
(–/+) Vaccination-induced immunity	4545	9	1.12	0.49–2.55	1.11	0.49–2.53

Adjusted models (age, sex, hospital, age, sex, any chronic condition, and patient-facing roles)

aHR adjusted hazard ratios, *CI* confidence interval, *HCWs* healthcare workers, *HR* hazard ratios, *PCR* polymerase chain reaction, *Ref* reference group, *SARS-CoV-2* Severe Acute Respiratory Syndrome Coronavirus 2, *VEBIS* Vaccine Effectiveness Burden and Impact Studies

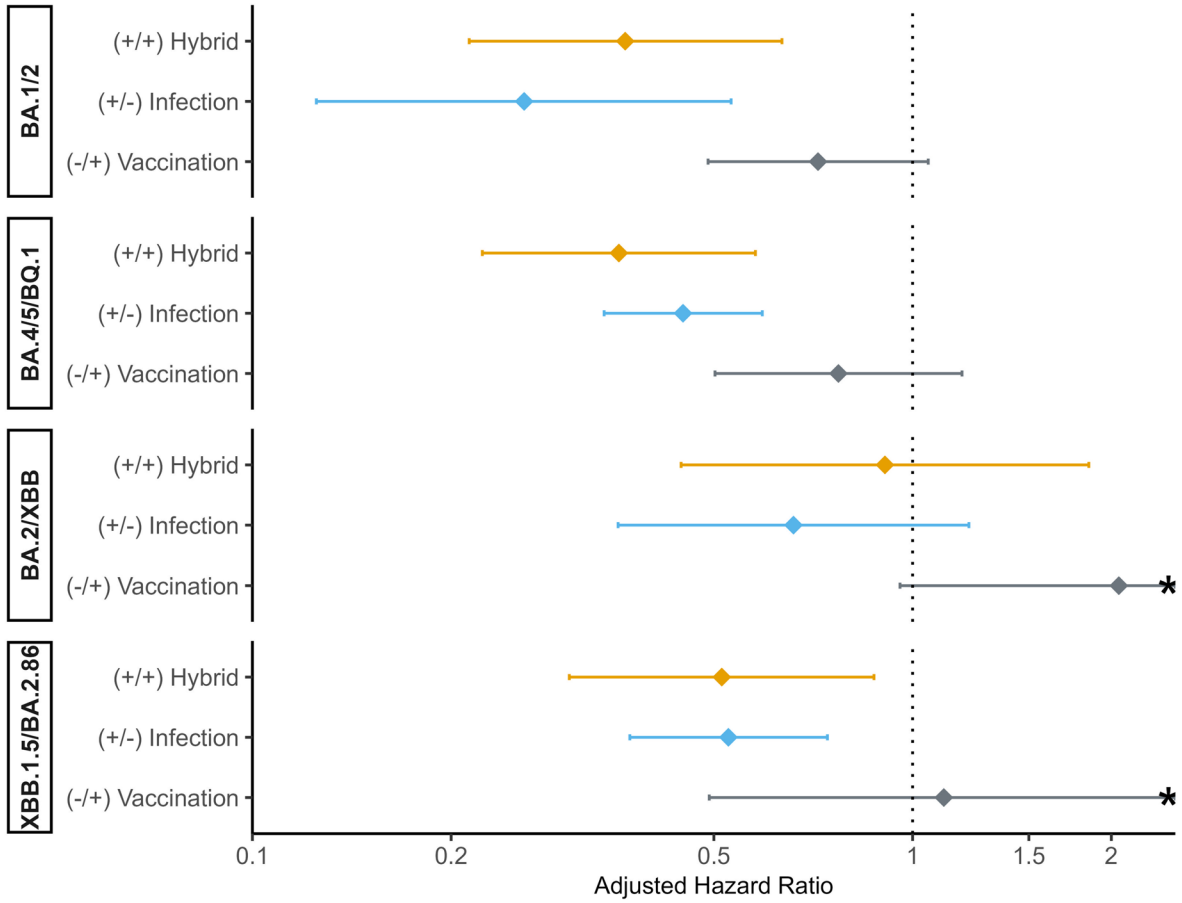
During the XBB.1.5/BA.2.86 Omicron post-pandemic period, the aHR of infection in the hybrid immunity exposure group was 0.51 (95%CI 0.30–0.87), and 0.53 (95%CI 0.37–0.76) in the infection-induced immunity exposure group. Finally, the aHR of the vaccination-induced immunity exposure group was 1.11 (95%CI 0.49–2.53) (Table 3, Fig. 1).

Hybrid immunity and infection-induced immunity were significantly higher than vaccination-induced immunity during Omicron BA.1/2, BA.4/5/BQ.1, and BA.2/XBB periods (adjusted p-values < 0.05). No significant differences were observed during Omicron XBB.1.5/BA.2.86 period (Additional file 3: Table S2).

Discussion

We estimated the protective effects of prior infection and recent vaccination, each and combined (i.e. hybrid immunity effect) against SARS-CoV-2 infection in a European multi-country HCW cohort, during different Omicron sub-lineage circulation periods. Our findings indicate that hybrid immunity conferred high levels of protection during the early circulation of pandemic Omicron sublineages (BA.1/2 and BA.4/5/BQ.1), and moderate protection during the later Omicron post-pandemic sublineages (XBB.1.5/BA.2.86). Comparable levels of protection were observed among HCWs from the infection-induced immunity exposure group, particularly during BA.1/2 and XBB.1.5/BA.2.86, although hybrid immunity offered added benefit during the BA.4/5/BQ.1 period. These results are partially explained by the shorter time since prior infection and recent vaccination in these periods, especially during BA.4/5/BQ.1 circulation. Conversely, our data suggest lower protection during the BA.2/XBB period compared with other periods, with protective effects generally weaker and with wide and overlapping confidence intervals. This coincided with possible stronger immune escape of the circulating variants, and longer average time since last infection and last booster vaccination.

Higher protection conferred by prior SARS-CoV-2 infection against new infections across the Omicron periods—regardless of vaccination status—has been documented in previous studies [11–14, 19–29]. A decline in the effectiveness of infection-induced immunity during later Omicron lineages has also been reported [23–25]. This pattern may reflect increasing time since prior infection across successive variant periods, as observed in our cohort.



Exposure groups	BA.1/2	BA.4/5/BQ.1	BA.2/XBB	XBB.1.5/BA.2.86
(+/+) Hybrid	38/42	25/120	31/19	25/40
(+/-) Infection	10/42	131/120	54/19	143/40
(-/+) Vaccination	225/42	29/120	18/19	9/40

Fig. 1 Forest plot, hybrid, prior SARS-CoV-2 infection-induced and COVID-19 vaccination protection against PCR-confirmed SARS-CoV-2 infection during the Omicron predominant circulation periods, multi-centre VEBIS HCW COVID-19 vaccine effectiveness study, 16 Dec 2021–21 May 2024. Yellow indicates hybrid immunity group; blue indicates prior infection with waned vaccination (≥ 180 days) and grey indicates vaccination-induced immunity (–/+) of no prior infection with recent (7–179 days) vaccination. The reference group is no prior infection and waned vaccination (≥ 180 days). * Indicates that values 95% confidence intervals truncated in adjusted hazard ratio > 2.5. The table in the figure presents the number of events for each exposure group and in the reference group. COVID-19: coronavirus disease 2019, HCW: Healthcare workers, SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2, VEBIS: Vaccine Effectiveness Burden and Impact Studies

Contrary to some studies [11, 14, 19–29], we did not find clear evidence of an additive effect of recent vaccination among individuals with prior infection, as most aHR point estimates in the hybrid immunity exposure group were lower than those in the infection-induced immunity group. However, we found a slightly but not statistically significant stronger effect of hybrid-induced immunity during the BA.4/5/BQ.1 periods compared with other periods. In our study, this may be explained by differences in the timing of vaccination and infection, waning of immune responses, and the degree of antigenic match between the vaccine and emerging variants. For example, in a previous study [30], we described the overall low vaccine effectiveness of the second booster dose compared to the first booster during the BA.2/XBB period, adjusted by prior infection. This is consistent with the lower effect in the hybrid immunity group in this study, which we explained by the increased immune evasion of XBB sub-lineage, immune imprinting, longer time since vaccination, and a high proportion of HCWs receiving

the monovalent original vaccine rather than the bivalent vaccine (original + BA.4/5) [30]. In addition, during the post-pandemic period, characterised by the predominant circulation of XBB.1.5 and BA.2.86, the sample size did not allow the analysis by sublineage using the four exposure groups. However, the low level of protection observed in the vaccination-induced immunity group and therefore in the hybrid immunity group is consistent with our previous work [31] where we reported the effectiveness of XBB.1.5-adapted vaccine used for seasonal vaccination in autumn 2024 to be 49% (95% CI − 8 to 76) before and − 11% (95% CI − 84 to 34) after the start of BA.2.86/JN.1 predominant circulation. We could not disentangle the effect of emerging sub-lineage circulation from the waning protection of vaccination [31].

In our study, the inclusion of asymptomatic or mild SARS-CoV-2 infection in the outcome may be a reason for not observing greater protection in the analysis using the hybrid immunity exposure group. It is expected that hybrid immunity or vaccination offers significantly better protection against severe than against mild disease or reinfection [13, 19, 32], particularly against severe infections caused by highly evasive variants. Indeed, serological studies suggest that both infection and vaccination enhance the humoral and cellular response, leading to a stronger and more durable immunity, as well as cross-protection against multiple strains [19, 27]. Furthermore, the level of protection likely varies with the sequence of vaccination and prior infection, as well as the number and type of exposures to different variants and vaccines [19, 27]. We were unable to evaluate these additional factors in our study.

The main strength of our study is the long follow-up period with regular contact (weekly or fortnightly) and PCR testing, regardless of symptoms. This approach minimised loss to follow-up and enabled the detection of asymptomatic and mild infections during each period of Omicron sub-lineage predominance, reducing the risk of missed cases. It also improved the completeness of prior infection data for participants re-entering the study following an infection. Indeed, the information on prior SARS-CoV-2 infections is particularly important for studies assessing the effectiveness of COVID-19 vaccines, as the absence of such data—or unreliable data—can bias effectiveness estimates, especially if the proportion of prior infection differs between vaccinated and unvaccinated individuals. In addition, stratification by Omicron sub-lineage predominant circulation period allowed us to account for temporal changes in vaccine timing and supply, evolving recommendations and background infection dynamics factors.

The main limitation of our study is the small sample size by analysis period, resulting in a lack of precision of the effect estimates and uncertainty in some findings. Caution is warranted in interpreting differences due to overlapping intervals and possible heterogeneity between sites in pairwise comparisons, and in generalising these findings. Furthermore, the limited sample size restricted our ability to estimate with precision the effects of prior infections vaccination type, vaccination at different times, specific linages, and to control for other potential confounders. Consequently, the possibility of residual confounding cannot be discarded. Nonetheless, although the number of HCWs recruited was small in some sites during certain sub-lineage predominant circulation periods, the study participants were representative of HCWs in their sites by vaccination status and clinical role. Second, as prior infection status is self-reported, there is a risk of recall bias or underreporting of prior infections, particularly among newly enrolled participants and asymptomatic SARS-CoV-2 infections, potentially leading to the misclassification of those reporting "no prior infection", and overestimation of the effects in these groups if differential among vaccinated and unvaccinated. Thirdly, we did not consider the serology results in infection detection as anti-N serology tests could not be performed in 4/18 sites, although anti-S serology was performed in all sites. Finally, although some sites conducted viral sequencing, we used national-level data available in ERVISS as a proxy for all sites, since the available data was insufficient to define sub-lineage predominance periods by site.

Conclusions

Our findings highlight the need to re-evaluate the COVID-19 vaccination strategy for healthcare workers in the post-pandemic era, as evidence suggests low protection within 180 days after vaccination, and additional immunisations in those with prior infection did not confer additional protection against asymptomatic or mild SARS-CoV-2 infection. However, as evidence also suggests that infection-induced immunity decreased in the post-pandemic period, and residual protection may be less effective against immune-evasive emerging sub-lineages, considering previous infection when designing vaccination campaigns should be done with caution.

COVID-19 vaccination of HCWs continues to be a critical strategy for preventing severe morbidity and mortality in this high-risk group, as well as reducing the impact of illness-related absence on essential services. Relying solely on infection control practices (ICP) and public health and social measures (PHSM) to prevent new infections in HCWs is a strategy that may not adequately protect the health workforce and health services during a future surge of SARS-CoV-2 infections. An integrated strategy combining timely

vaccination with reinforcement of ICP, in periods of high incidence and when a new variant emerges, should still be recommended for HCWs. Future studies will be needed to assess immunity in relation to updated formulations, including JN.1-adapted, KP-adapted, and other subsequent adaptations.

Abbreviations

AgRDT	Antigen detection rapid diagnostic test
aHR	Adjusted hazard ratios
Anti-N	Antibodies to the Nucleocapsid protein
Anti-S	Antibodies to the Spike protein
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CT	Computerised tomography
EMA	European Medicines Agency
ERVISS	European Respiratory Virus Surveillance Summary
EU	European Union
HCWs	Healthcare workers
HR	Hazard ratios
IQR	Interquartile range
PCR	Polymerase chain reaction
PHEIC	Public Health Emergency of International Concern
RT-PCR	Reverse Transcription Polymerase Chain Reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
VEBIS	Vaccine Effectiveness Burden and Impact Studies

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-025-04503-2.

Additional file 1: Figures S1-S3. Figure S1 – [Participation of the hospitals by calendar month follow-up period, multi–centre VEBIS HCW COVID-19 vaccine effectiveness study, 16 Dec 2021–21 May 2024]. Figure S2 – [Data inclusion flow chart for analysis pandemic Omicron period and post-pandemic Omicron period, multi–centre VEBIS HCW COVID-19 vaccine effectiveness study, 16 Dec 2021–21 May 2024]. Figure S3 – [Proportions of SARS-CoV-2 Omicron sub-lineage in sequenced samples over time and by country in the multi-centre VEBIS HCW vaccine effectiveness study: Analysis of ERVIS data, Dec 2021-May 2024].

Additional file 2: STROBE Statement—checklist of items that should be included in reports of observational studies.

Additional file 3: Table S1-S2. Table S1 – [Participant HCWs vaccination and prior infection characteristics at the start of each Omicron sub-lineage predominant circulation period, multi-centre VEBIS HCW COVID-19 vaccine effectiveness study, 16 Dec 2021–21 May 2024]. Table S2 – [Multiple comparison: hybrid, prior SARS-CoV-2 infection and COVID-19 vaccination protection against PCR-confirmed SARS-CoV-2 infection during the Omicron sub-lineage predominant circulation, multi-centre VEBIS HCW COVID-19 vaccine effectiveness study, 16 Dec 2021–21 May 2024].

Acknowledgements

We thank all participants, hospital staff, and study investigators not listed above for their efforts to conduct this study. We are also grateful to the following study team members:

Croatia: Josipa Kuzle, Anita Jurić, Ljiljana Antolašić, Ljiljana Milašinčić, and Martina Zajec

Estonia: Kadri Kõivumägi, Natalia Nikitina, Anna Aleksandrova, and Anastassia Kuželko

Ireland: Irene Flynn Dowling, David Byrne, Noeleen Maher, and Nicola Murphy

Italy: Paolo Adorno, Giuliana Favara, Viviana Frontini, Angelo Gambera, Patrizia Grassi, Claudia La Mastra, Antonio Lazzara, Andrea Maugeri, Anna Rita Mattaliano, Simone Martello, Arturo Montineri, Milena Nardi, Ilenia Palermo, Gabriele Rapisarda, Roberta Magnano San Lio, Belatoo Savitree, Guido Scalia, Antonino Scaltrito, Rosario Vinci, and Ilaria Beretta

Latvia: Elina Dimina and Inese Gobina

Poland: Aleksandra Kulesza

Portugal: Ana Catarina Dias, Filipe Pimenta, Rui Pedro Lopes, Pedro Nunes, Filipa Chaves, Catarina Barradas, Ana João Santos, and João Faro Viana, and, Sara Ramalhete

Romania: Gratiela Tardei, Simona Maria Ruta, Catalina Pascu, Sorin Dinu, Alina Ivanciuc, Iulia Bistriceanu, Mihaela Oprea, Maria Elena Mihai, Valentina Comanici, and Alina Angelica Belivaca.

Spain: Lourdes Roc Alfaro, Sonia Usón Lucea, Beatriz Órpez Villen, Víctor Cantín-Lahoz, Emilia Ferrer López, María Pilar Martínez López, Miriam Infante Garza, Pilar Díaz Díaz, Maria Pilar Rubio Pastor, Rosa María García Cester (HUMS, Zaragoza); Jesus Marquez, Ana Codina, Cristina Jou (Biobank- Hospital Sant Joan de Deu), Marta Cubells and Felipe Pérez-Soler (Clinical Research Unit-Institut de Recerca Sant Joan de Deu)

We also thank Angela Mary Rose and Esther Kissling for their valuable comments on the draft manuscript, as well as Valerie Nancey and Djenaba Bamba for their support.

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Hanna Sepp, Lisa Domegan, Joan O'Donell, Maeve Kernan, Anne Moriarty, Conor Moran, Giulia De Angelis, Giulia Menchinelli, Cinzia Recine, Silvia Zelli, Benedetta Falasca, Silvia Lamonica, Zrinka Bošnjak, Ana Budimir, Tvrtko Žarko, Božena Rašić, Marko Ćurković, Porin Makarić, Senka Repovečki, Kornelija Petir, Irena Tabain, Tatjana Vilibić Čavlek, Janis Meisters, Laura Zemite, Hilda Darta Snipe, Estere Ergle, Ana Palmira Amaral, João Almeida Santos, Daniela Dias, Licínia Gomes, Miguel Lança, Henrique Carvalho, Jose Alves, Daniel R. Codreanu, Alexandru Marin, Amaresh Pérez-Arguello, Iolanda Jordan, Juan Jose Garcia-Garcia, Antonio Rezusta López, Alexander Isaias Tristancho Baró, Ignacio Ezpeleta Ascaso, Sandra Dueñas Jollard, Noelia Terren Marco, Tamara Valero Vicente, Nieves Felisa Martínez Cameo, Yolanda Gracia Grataloup, David Martínez Mateos, Beatriz Gilaberte Angós, Diego Ortega Larrea, María Pilar Abad Alejaldre, Cristina Carrasco Carbó, Carmen Martínez Giménez, Maria Gemma Martínez Andrés, Bruno del Moral Redolat, Ana Maria Sabio Blasco, Raquel Guiomar, Aryse Melo, Francisco Pozo, Iris Ganser, Cristina López, Albert Prats, and Antony Nardone.

Authors' contributions

M.R.C supported the coordination of the VEBIS HCWs network and study design. She led the statistical plan of analysis, contributed to data cleaning, conducted the analysis, interpreted and reviewed results, wrote the manuscript, and approved the final version of the manuscript. R.M1 contributed to the statistical plan of analysis and data cleaning, conducted the data analysis, helped interpret results, contributed to manuscript writing, and approved the final version of the manuscript. K.B and S.B were involved in the study design, interpretation of results, and reviewing all manuscript versions. C.S coordinates the VEBIS HCWs network. She was involved in the study's original methodological design (generic protocol). She supported the statistical plan of analysis, reviewed and interpreted results, wrote the manuscript, and approved the final version Z.L.M, A.U, C.B, C.F, P.B, R.M2, V.Z, D.Z, K.S, V.G, C.P.P, M.C1, R.M.H, M.C2, M.L.M, G.P, L.L, J.M, L.F, A.S, K.G.D, I.A, D.G, A.M, S.A.F, M.L, P.S, 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.

Funding

This study was funded by the European Centre for Disease Prevention and Control through "Vaccine Effectiveness, Burden and Impact Studies" (VEBIS) Lot 2 "Assessment of COVID-19 and influenza vaccine effectiveness among healthcare workers" framework contract ECDC/2021/017.

Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The planning, conduct and reporting of the current study were in line with the Declaration of Helsinki, as revised in 2013 (https://www.wma.net/polic

ies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects). Informed consent was obtained from each participant at the enrolment in the study. The study was approved by the Ethical review committees from each hospital: Eticko Povjerenstvo Hrvatskog zavoda za javno zdravstvo (HZJZ) Croatia, Zagreb: 381-15-21-3; Tartu Ülikooli inimuuringute eetika komitee, 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, Dipartimento di Sicurezza e Bioetica, Rome, Italy : 00372/23; Università degli Studi di Milano-Bicocca presented same approval as Policlinico Gemelli, Università Cattolica del Sacro Cuore, Rome, Italy from the National Institute of Infectious Diseases, Spalanzzani IRCCS; 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; Ethic Committee Name: Komisja Etyki I Nadzoru nad Badaniami na Ludziach I Zwierzetach przy Centralnyum Szpitalu Klinicznym MSWIA w Warszawie, Poland, Warszawie: 15/2022; Comissão de Ética para a Saúde, INSA Doutor Ricardo Jorge, Portugal: INSA-IM60_05; Comisia de Etica a Spitalului Clinic de Boli Infectioase si Tropicale "Dr. Victor Babes", Romania: 14420; Comisia Locala de Etica a Spitalului Universitar de Urgenta Militar Central "Carol Davila", Romania: 646; Ethic Committee Name: Comisia de Etica a Cercetarii-Dezvoltarii din cadrul Institutului National pentru Sanatatea Mamei si Copilului "Alessandrescu-Rusescu", Approval Code: 1464, Approval Date: 18 January 2023; Comité de Ética de la Investigación de la Comunidad Autónoma de Aragón (CEICA), HU Miguel Servet, Zaragoza, Spain: PI21-176 and PI22/483; Comité De Ética De La Investigación Con Medicamentos, Sant Joan de Déu, Fundacio de Recerca, Barcelona, Spain: 17/2023.

Consent for publication
Not applicable.

Competing interests
M.L.M, A.M, and L.C reported receiving additional funds from the European Union Research and Innovation programme Horizon Europe (ISIDORe – Grant Agreement Number 101046133) for conducting local SARS-CoV-2 sequencing. CPP and S.A.F reported speaker fees from and participation in the advisory boards of Pfizer and M.S.D. S.A.F reports also participating in the Advisory Board of Gilead. C.M.A reported speaker fees from M.S.D, Pfizer and Sanofi. J.S reported support for attending the ESID conference 2022 from Takeda Pharmaceutical. R.H and S.P reported a grant attributed to their institution on "PSCD Longitudinal evaluation of SARS-CoV-2 immune status post-natural infection and post-vaccination". C.M.A reported speaker fees from M.S.D. All other authors declare no conflicts of interest related to this work.

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Received: 4 August 2025 Accepted: 7 November 2025
Published online: 29 December 2025

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