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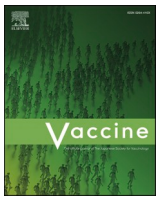

Relative effectiveness of the second booster COVID-19 vaccines against laboratory confirmed SARS-CoV-2 infection in healthcare workers: VEBIS HCW VE cohort study (1 October 2022-2 May 2023)

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Abbreviations: COVID-19, coronavirus disease; ECDC, European Centre for Disease Prevention and Control; HCW, healthcare worker; PCR, polymerase chain reaction; rVE, relative vaccine effectiveness; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; VE, vaccine effectiveness; VEBIS, Vaccine Effectiveness, Burden and Impact Studies project.

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ABSTRACT

Introduction: Repeated COVID-19 booster vaccination was recommended in healthcare workers (HCWs) to maintain protection. We measured the relative vaccine effectiveness (rVE) of the second booster dose of COVID-19 vaccine compared to the first booster, against laboratory-confirmed SARS-CoV-2 infection in HCWs.

Methods: In a prospective cohort study among HCWs from 12 European hospitals, we collected nasopharyngeal or saliva samples at enrolment and during weekly/fortnightly follow-up between October 2022 and May 2023. We estimated rVE of the second versus first COVID-19 vaccine booster dose against SARS-CoV-2 infection, overall, by time since second booster and restricted to the bivalent vaccines only. Using Cox regression, we calculated the rVE as (1-hazard ratio)*100, adjusting for hospital, age, sex, prior SARS-CoV-2 infection and at least one underlying condition.

Results: Among the 979 included HCWs eligible for a second booster vaccination, 392 (40 %) received it and 192 (20 %) presented an infection during the study period. The rVE of the second versus first booster dose was −5 % (95 %CI: −46; 25) overall, 3 % (−46; 36) in the 7–89 days after receiving the second booster dose. The rVE was 11 % (−43; 45) when restricted to the use of bivalent vaccines only.

Conclusion: The bivalent COVID-19 could have reduced the risk of SARS-CoV-2 infection among HCWs by 11 %. However, we note the limitation of imprecise rVE estimates due to the proportion of monovalent vaccine used in the study, the small sample size and the study being conducted during the predominant circulation of XBB.1.5 sub-lineage. COVID-19 vaccine effectiveness studies in HCWs can provide important evidence to inform the optimal timing and the use of updated COVID-19 vaccines.

1. Introduction

At the end of November 2021, the Omicron variant of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus that caused the coronavirus disease 2019 (COVID-19) pandemic was detected in Europe [1]. The Omicron variant introduction led to a surge in infections in Europe that occurred in waves every 2–3 months, temporally associated with the increased circulation of different sub-lineages of this variant (BA.1–5 and their descendants and recombinants) and seasonal population mixing patterns [2]. Detected in Europe in late 2022, the Omicron XBB variant, a BA.2 descendant [3] and its sub-lineages including XBB.1.5 and other strains with similar Spike protein profiles [4], was characterised by increased transmissibility [4–6], lower pathogenicity [3] and enhanced immune evasion from vaccination and previous SARS-CoV-2 infection compared to previously circulating variants [4,6,7].

The composition of the COVID-19 vaccines included in national vaccination programmes was adapted over time according to the changes in SARS-CoV-2 variant and sub-lineages circulation [8]. Spike-based monovalent original strain vaccines were used for primary course and first booster vaccination between December 2020 and September 2021. Bivalent vaccines containing antigens of the original and BA.1 or BA.4–5 strains were authorised in the European Union from August 2022 [8] and gradually replaced the monovalent original strain vaccines in the autumn of 2022 for booster vaccinations.

Real-life COVID-19 vaccine effectiveness (VE) is important to measure due to changing epidemiology of the SARS-CoV-2 infection related to continuously emerging variants and sub-lineages, as well as for the short duration of protection due to waning of protective antibodies [9]. However, these factors along with low vaccine uptake make the evaluation of the performance of the COVID-19 vaccines in real conditions challenging.

The Vaccine Effectiveness Burden and Impact Studies (VEBIS) is a platform for multicentre European VE and other studies funded by the European Centre for Disease Prevention and Control (ECDC). One of the components of this platform aimed at assessing the effectiveness of the COVID-19 vaccines among HCWs (VEBIS HCW study) [10]. Healthcare worker (HCW) cohorts provide a unique opportunity to study the effect of COVID-19 vaccines in a well-defined and easy to track group consisting mostly of healthy adults in working age. One of the rationales for this study was the limited knowledge on COVID-19 VE against symptomatic and asymptomatic infection at the time of set-up. HCWs represent a priority group for COVID-19 vaccination because they are at a higher risk of SARS-CoV-2 infection [11], and can transmit the infection, also when asymptomatic, to susceptible patients that can develop severe disease. In addition, HCWs need to be protected in order to maintain essential healthcare services [11–13] during the COVID-19 waves.

This work presents the results of the VEBIS HCW study aimed at measuring the relative effectiveness (rVE) of COVID-19 vaccine second booster dose versus the first booster dose, against laboratory-confirmed SARS-CoV-2 infection, in eligible HCWs between 1 October 2022 and 2 May 2023.

2. Methods

2.1. Study procedures

The study protocol and a rVE interim analysis of the first booster dose have been published elsewhere [10,14]. In brief, we conducted a dynamic prospective longitudinal multicentre cohort study among HCWs eligible for COVID-19 vaccination from 12 hospitals in seven countries participating in the VEBIS HCW study between 1 October 2022 and 2 May 2023. At each study site, we included HCWs from all categories of staff in whom vaccination was not contraindicated, did not present with special recommendations for vaccination (i.e. immunocompromised participants with three-dose primary course), did not present an immunisation event (vaccination or infection) in the previous three months and who provided informed consent. At recruitment, we collected a nasopharyngeal or saliva sample for RT-PCR testing for SARS-CoV-2 infection (Fig. 1), and collected demographic, clinical (vaccination history, prior infection with SARS-CoV-2) and in-hospital- and community-related behavioural data. At follow-up, participating HCWs provided weekly/fortnightly samples to test for SARS-CoV-2 infection using RT-PCR and filled in a weekly questionnaire to record changes in vaccination status and professional and community risk for infection. Blood samples were taken every 8–12 weeks and tested for at least anti-spike-protein antibodies.

2.2. Outcome and exposure definitions

The primary outcome was a confirmed SARS-CoV-2 infection detected by RT-PCR in any participant, regardless of symptoms. Secondary outcomes of confirmed SARS-CoV-2 infections were ascribed as either asymptomatic or symptomatic COVID-19 groups. Symptomatic COVID-19 were participants with RT-PCR confirmed SARS-CoV-2 infection reporting at least one clinical criterion to conform with the ECDC 2021 possible case definition of COVID-19 (cough, fever, shortness of breath/dyspnoea, anosmia, ageusia/dysgeusia) 14 days before to

7 days after a positive RT-PCR test performed during the study. If a participating HCW was tested outside the study, the information was retrieved and included in the study. Participating HCWs who seroconverted during the study with regular negative virology tests were completely excluded from the study.

The exposed group included HCWs who were eligible for a second booster dose (i.e. had received the first booster dose ≥90 days before) and who were fully protected after having received the second booster ≥7 days before, according to the recommendations from the main product characteristics. The reference group comprised HCWs vaccinated ≥90 days since the first booster dose, received after a two-dose primary course vaccination. In a sensitivity analysis, we included HCWs who received a bivalent vaccine as their second booster dose, excluding from the reference group HCWs who received a bivalent vaccine as their first booster.

HCWs vaccinated with primary course only, those who were partially vaccinated (i.e. receiving one or two-dose vaccination from ≥14 days after receiving the first dose to <14 days after the second dose) or who were unvaccinated (i.e. who had received no dose of vaccine or who had received the first dose of a vaccine <14 days before) were not eligible for this study. During the course of the study, the vaccination status of HCWs could change from vaccinated with the first to vaccinated with the second booster dose.

2.3. Data analysis

Each participating HCW began contributing person-time at risk: 1) from 1 October 2022 if enrolled before this date or the date of start of the vaccination campaign (Fig. 1) if later at study site; 2) the date of enrolment if after this date; 3) 60 days after a RT-PCR-confirmed SARS-CoV-2 infection [15]; or 4) 90 days from the first booster dose or 7 days from the second booster COVID-19 vaccination, whichever was the latest. Person-time at risk ended at SARS-CoV-2 infection (the date of onset of symptoms from a SARS-CoV-2 infection, or of the positive RT-PCR test in the absence of symptoms), at the last follow-up test if loss of follow-up or the study censor date (2 May 2023).

Using Cox regression, we calculated the relative vaccine effectiveness (rVE) as (1-hazard ratio of second booster vaccination and first booster vaccination)*100, adjusted for hospital, age (modelled as second degree polynomial), sex, report of at least one underlying condition, and self-reported a SARS-CoV-2 infection prior to the start date of this analysis at the hospital level. Hazard ratio was calculated by comparing the hazard rate of SARS-CoV-2 infection in the HCWs who received the second booster to those who received the first booster. Calendar time was used as the underlying time in the Cox regression.

We present the rVE results against any infection, only symptomatic and only asymptomatic infections, and stratified by self-reported prior SARS-CoV-2 infection before recruitment, by predominant circulation of Omicron sub-lineages BA.4/5/BQ1 (1 October – 31 December 2022) and XBB.1.5 (1 January – 2 May 2023). We also measured rVE by time since second booster dose (7–89, ≥90 days). In the sensitivity analysis, we measured rVE of the bivalent COVID-19 vaccine by excluding HCWs who received the vaccination with monovalent original COVID-19 vaccine for their second booster dose. All analyses were performed using Stata 17 (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC.).

Ethical approval was obtained from the ethical review committees of each participating hospital prior to the start of the study. Informed consent was obtained from each participant by the hospital study teams.

3. Results

Twelve hospitals from seven countries (Estonia, Ireland, Latvia, Poland, Portugal, Romania and Spain) were included in the VEBIS HCW cohort during the study period. Of the 1717 HCWs from the 12 hospitals that ever participated in the VEBIS HCW study, 973 (57 %) HCWs (range per hospital 14–151) were followed up during the study period. The included HCWs were followed up for a total 108,010 person-days between October 2022 and May 2023 (Fig. 1) with a median follow-up time of 70 days (interquartile range (IQR) of 43–138; maximum follow-up time 213 days), after applying inclusion and exclusion criteria and further excluding participants not eligible for the second booster dose vaccination (Fig. 2). A total of 91 HCWs (9 %) were lost to follow-up and all hospitals but three replaced them.

Included participant HCWs were mostly female (825, 85 %), with a median age of 45 years (IQR 36–53 years), 236/633 (37 %) reporting at

		Hospital participation							Testing		Start of second booster vaccination campaign
		2022			2023				Timing	Sample type	
		Oct	Nov	Dec	Jan	Feb	Mar	Apr			
Estonia	Hospital 1								weekly	saliva	Dec 2021
	Hospital 2								weekly	saliva	Jul 2022
Ireland	Hospital 1								weekly	NP	Sep 2022
	Hospital 2								weekly	NP	Nov 2022
Latvia	Hospital 1								fortnightly	NP	Sep 2022
	Hospital 2								fortnightly	NP	Sep 2022
Portugal	Hospital 1								weekly	saliva	Oct 2022
Poland	Hospital 1								weekly	saliva	Sep 2022
Romania	Hospital 1								weekly	NP	May 2022
	Hospital 2								weekly	NP	Jan 2022
Spain	Hospital 1								weekly	saliva	Oct 2022
	Hospital 2								weekly	NP	Sep 2022

NP – Nasopharyngeal sample

Fig. 1. Participating hospitals by study time, VEBIS HCW study, 1 October 2022–2 May 2023.
NP – Nasopharyngeal sample.

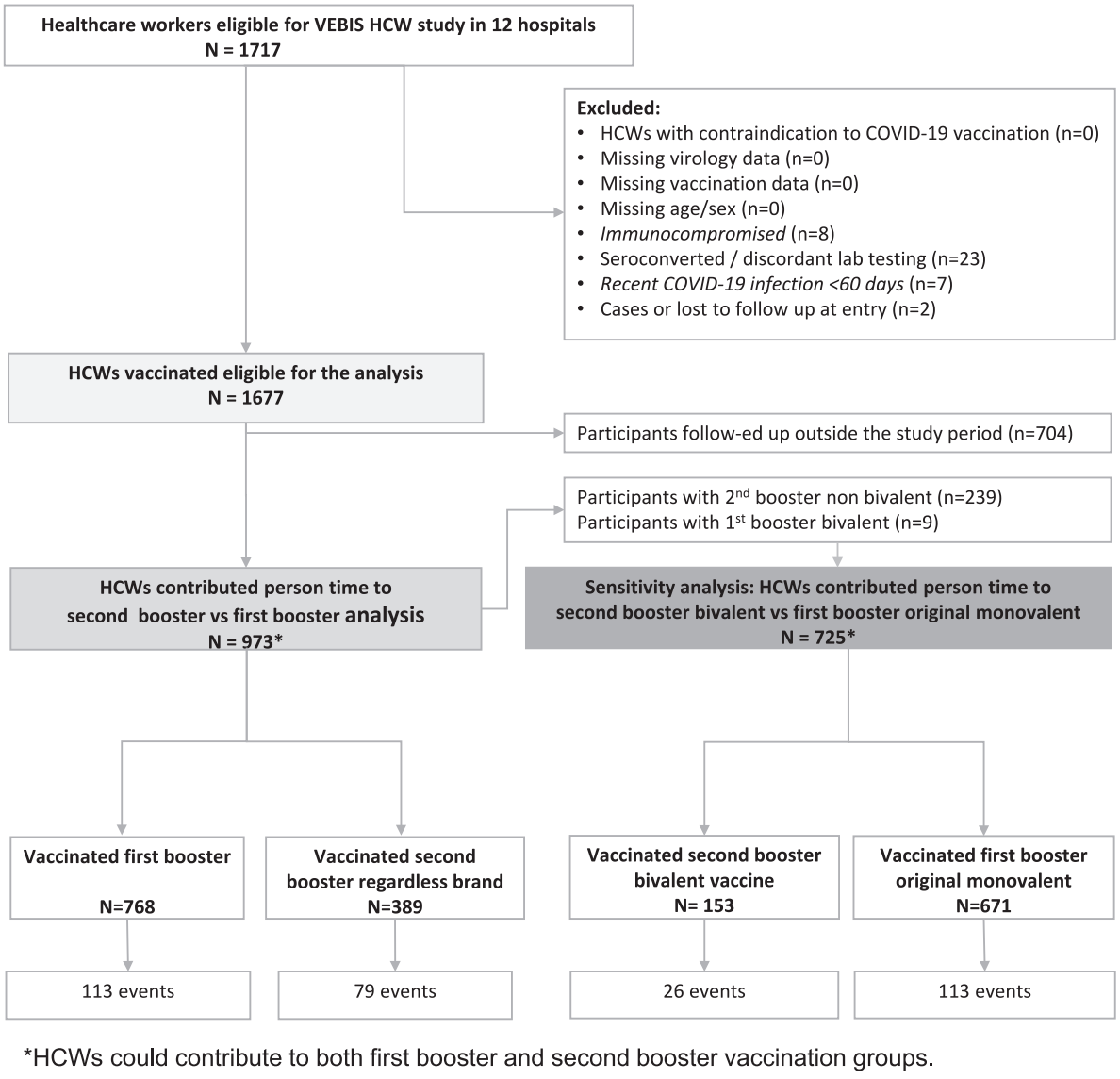

Fig. 2. Exclusion flowchart, multi-country VEBIS HCW Study, 1 Oct 2022–2 May 2023.

least one underlying condition, and 575 (60 %) were in a clinical role: 196 (20 %) medical doctors and 379 (40 %) nurses. A total of 771/959 (74 %) HCWs reported a prior SARS-CoV-2 episode (Table 1).

Of the 973 HCWs eligible for a second booster dose, 389 (40 %) subsequently received it. The HCWs vaccinated with a second booster had a median age of 47 years, and the other characteristics were similar to those who did not receive a second booster (Table 1). The most used vaccine brand for a second dose was Comirnaty bivalent (174, 45 %), followed by Comirnaty original monovalent (135, 35 %).

A total of 192 confirmed infections were detected in 187 (19 %) HCWs: 93 (48 %) before 31 December 2022 and 99 after this date. The five HCW with two infections were re-entered into the cohort 60 days after their first infection. The incidence rate was the highest in December 2022 and March 2023 (Fig. 3). Ninety-one (47 %) positive samples were sequenced, 39 (43 %) were BA.4/5 and related, 28 (31 %) were BA.2/XBB and 24 (26 %) were XBB.1.5 (Fig. 3). Twenty-two (13 %) infected HCWs reported performing aerosol generating procedures, 14 (8 %) reported contact with a case at home, 12 (7 %) contact with a case at the hospital, and 111 (60 %) reported being vaccinated with the first booster dose and 76 (41 %) with the second booster. Among the 192 infections detected, 102 were symptomatic. Similar profiles were observed among HCWs included in the sensitivity analysis of those vaccinated with a bivalent second booster dose (Table 2).

The rVE of the second COVID-19 booster dose against SARS-CoV-2 infection (asymptomatic and symptomatic) compared to the first booster dose in the primary analysis was −5 % (95 %CI: −44; 25) overall; 29 % (−15; 56) before 31 December 2022 and − 54 % (−146; 3) after this date (Table 3). The rVE against asymptomatic infection was 12 % (−44; 42) overall; 60 % (9; 83) and − 52 % (−187; 20) before and after 31 December 2022, respectively. The rVE against symptomatic infection was −19 % (−87; 24) overall; 2 % (−80; 46) and − 53 % (−201; 22) before and after 31 December 2022, respectively. Among HCWs with no prior SARS-CoV-2 infections, the rVE was 16 % (−55; 54) overall; 31 % (−55: 69) and − 2 % (−174; 62) before and after 31 December 2022, respectively (Table 3). By 7–89 days since the second booster dose, the rVE against any infection was 3 % (−46; 36); 32 % (−30; 65) against asymptomatic infection and − 27 (−116; 25) against symptomatic infection (Table 4).

In the sensitivity analysis considering only those HCWs that received the bivalent vaccine as their second booster dose as exposed, the rVE against any infection was 11 % (−43; 45) overall for the whole study period, 24 % (−49; 61) and − 13 % (−129; 44) before and after 31 December 2022, respectively. The overall rVE was 19 % (−67; 61) against asymptomatic infections, and 69 % (10; 89) in HCWs with no

Table 1
Characteristics of participant HCWs in the primary and sensitivity analysis, VEBIS HCW study, 1 Oct 2022–2 May 2023.

Characteristic	Second booster compared to first booster, regardless vaccine brand				Second booster bivalent vaccine compared to first booster			
	Eligible for second booster dose		Received the second booster dose		Eligible for second booster dose bivalent vaccine		Received second booster dose bivalent vaccine	
	TOTAL (n = 973)	%	TOTAL (n = 389)	%	TOTAL (n = 725)	%	TOTAL (n = 153)	%
Gender								
Female	825	84.8	314	80.7	625	86.2	124	81.0
Age (years)								
Median [p25–75]	45	36–53	47	39–55	44	35–52	46	39–54
19–35	220	22.6	60	15.4	177	24.4	22	14.4
35–40	117	12.0	45	11.6	90	12.4	20	13.1
40–44	144	14.8	58	14.9	109	15.0	23	15.0
45–49	165	17.0	65	16.7	129	17.8	29	19.0
50–54	128	13.2	58	14.9	90	12.4	21	13.7
55–70	199	20.5	103	26.5	130	17.9	38	24.8
Role								
Medical Doctor	196	20.4	87	22.7	139	19.4	30	19.6
Nurse	379	39.5	139	36.3	297	41.4	60	39.2
Allied professionals	46	4.8	18	4.7	38	5.3	10	6.5
Laboratory	48	5.0	14	3.7	38	5.3	6	3.9
Administration/Reception	160	16.7	72	18.8	109	15.2	23	15.0
Ancillary	27	2.8	10	2.6	20	2.8	5	3.3
Other	104	10.8	43	11.2	77	10.7	19	12.4
Underlying conditions*								
At least one	236	37.3	97	39.0	171	35.8	37	37.4
Previous COVID-19 episodes								
Yes	708	73.8	263	69.0	550	76.7	116	76.8
No	251	26.2	118	31.0	167	23.3	35	23.2
Missing	14	1.4	8	2.1	8	1.1	2	1.3

* Underlying conditions information collected: diabetes, cardiovascular disease (excluding hypertension), hypertension, immunodeficiency/organ transplant, lung disease (excluding asthma), asthma, cancer, morbid obesity, renal disease, liver disease, rheumatological disease, neuromuscular disease.

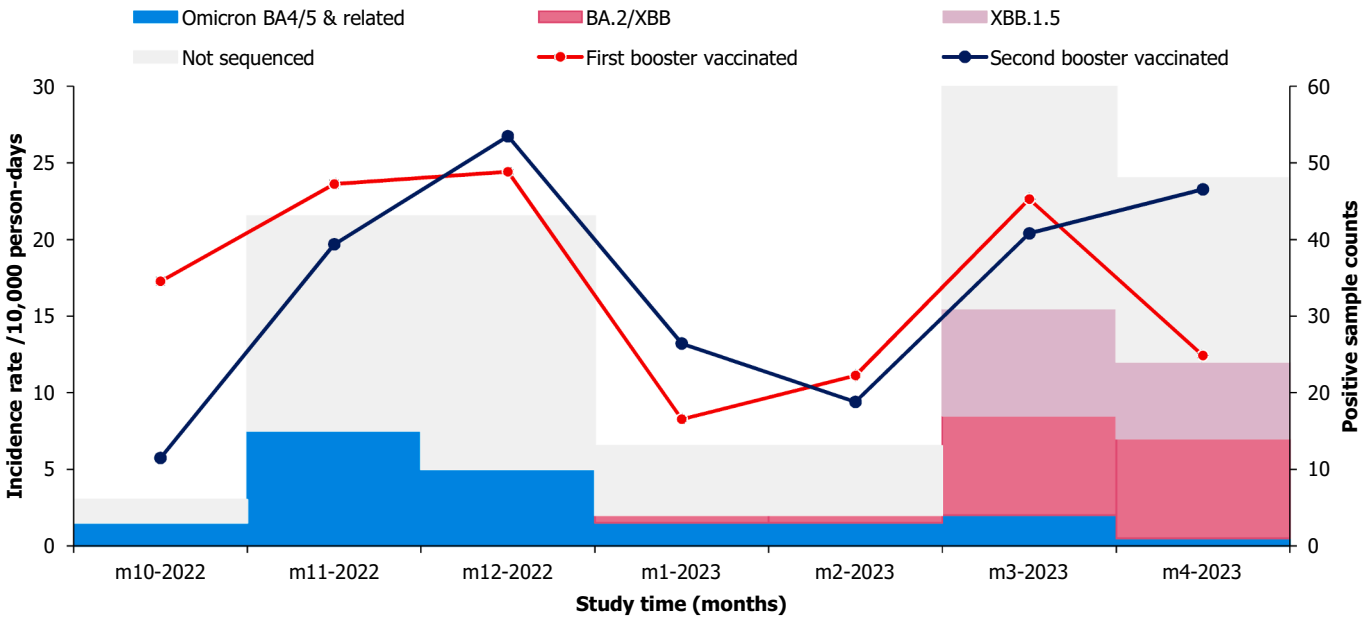

Fig. 3. Incidence rate by month of participation in the study, vaccination status and positive sample sequenced, multi-country VEBIS HCW study, October 2022–April 2023.

prior SARS-CoV-2 infection reported (Table 3). The number of events in this analysis did not allow a more in-depth analysis by time since vaccination.

4. Discussion and conclusion

We presented the findings of a prospective cohort study aimed at measuring the rVE of a second COVID-19 booster dose among HCWs of 12 hospitals from seven European countries, followed up between October 2022 and May 2023. Our findings suggest that overall, during the study period, the second COVID-19 booster dose vaccination did not seem to add to the residual protection of the first booster dose against SARS-CoV-2 infection in this high-risk population. However, a second booster of COVID-19 vaccine seems to offer additional protection in HCWs that had not experienced a prior SARS-CoV-2 episode and against asymptomatic infection, particularly within 90 days of vaccination and if vaccinated with the COVID-19 bivalent vaccine.

When we restricted the study to the period before 31 December 2022

Table 2
Characteristics of HCWs with a SARS-CoV-2 infection in the primary and sensitivity analyses, VEBIS HCW study, 1 October 2022–2 May 2023.

Characteristic	Second booster compared to first booster, regardless vaccine brand ($n = 187$ HCWs)		Second booster bivalent vaccine compared to first booster ($n = 136$ HCWs)	
	Number	%	Number	%
Age (median, range)	46	38–54	45.5	36.5–53
Gender (female)	163	87.2	122	89.7
Reported at least one underlying condition	49	26.2	32	23.4
Professional role				
Medical doctor	33	17.7	19	14.1
Nurse/nurse assistants	80	43.0	63	46.7
Administration/reception	32	17.2	19	14.1
Other	41	21.9	34	25.0
Contact COVID-19 case				
At home	14	8.2	12	9.4
At work	12	7.1	9	7.0
Applied AGP*	22	12.9	15	11.7
Vaccination				
First booster	111	59.5	111	81.6
Second booster	76	40.6	25	18.4

* AGP: Aerosol generating procedure.

(less than 75 % XBB circulation in the participating countries) or to the use of bivalent vaccine, the overall rVE point estimates were similar to other studies [16–18]. Bivalent vaccines were first authorised in Europe in August–September 2022 (bivalent Original/Omicron BA.1) and September–October (Original/Omicron BA.4–5) [8] when many HCWs had already received booster doses with the monovalent original vaccine, according to country-specific recommendations. In our study, less than a half of HCWs were vaccinated with a second booster dose, and less than half of these were vaccinated with bivalent vaccine, partly explaining the lack of additional protection compared to the first booster dose overall, and the low protection 7–89 days after vaccination. This adds to the body of evidence that COVID-19 vaccine antigen composition needs to be updated to enhance vaccine-induced immune responses to circulating strains and deployed ahead of any potential surge of disease [19].

We report a lower overall rVE of the second booster dose than reported in other studies [16,17,20,21]. These studies were conducted during summer–autumn 2022, soon after the introduction of the second booster in the respective countries, when the Omicron XBB was not predominant. During our study, we noted the predominant circulation of the former variant of concern Omicron B.1.1.529 + BA.4/5/BQ1 as well as the variant of interest XBB and its offsprings, including XBB.1.5. The XBB.1.5 sub-lineage was first detected in the VEBIS HCW participating countries at the end of November 2022 (week 47 in Spain, 48 in Ireland and 49 in Portugal and Romania) and rapidly increased in January–February 2023 (GISAID, the global data science initiative, https://gisaid.org/hcov19-variants/). This variant of interest was reported to evade the vaccine protection [6,7] that could explain the lower rVE point estimates reported in our study after 1 January 2023.

Although our rVE estimates present wide confidence intervals and the results need to be interpreted with caution, they are in line with the UK study [16] which also reported that a second COVID-19 vaccine booster dose was associated with a greater protection against asymptomatic than symptomatic infection and for those with no prior SARS-CoV-2 infection compared to those with prior infection. In the SIREN study, individuals with asymptomatic infection had been previously infected more recently than those with symptomatic infection, which could be an explanation for the added protection in the asymptomatic group [16]. A recent past infection confers an extra layer of protection to the individual, and the additional protection captured in a rVE estimate will therefore by nature be smaller in this group. Lower rVE in those previously infected may be also related to immune imprinting [22]

Table 3
Adjusted relative vaccine effectiveness of the COVID-19 booster by exposure, outcome, and self-reported prior SARS-CoV-2 infection and by different periods corresponding to predominant circulation of Omicron BA4/5 and XBB1.5 sub-lineages, VEBIS HCW study, 1 Oct 2022–2 May 2023.

Outcome / Stratification	Second booster compared to first booster, regardless vaccine brand							Second booster bivalent vaccine compared to first booster						
	Received first booster dose			Received second booster dose			Fully adjusted rVE	Received first booster non-bivalent			Received second booster bivalent			Fully adjusted rVE
	N	PT	e	N	PT	e	rVE% (95 %CI)	N	PT	e	N	PT	e	rVE% (95 %CI)
Any infection	768	64,242	113	389	43,768	79	−5 (−46; 25)	671	60,795	113	153	18,449	26	11 (−43; 45)
By infection type														
Asymptomatic	768	64,242	52	389	43,768	38	12 (−44; 46) 46)	671	60,795	52	153	18,449	11	19 (−67; 61)
Symptomatic	768	64,242	61	389	43,768	41	−19 (−87; 24)	671	60,795	61	153	18,449	15	3 (−84; 48)
By prior infection														
No	178	11,454	32	118	11,827	35	16 (−55; 54)	153	10,704	32	35	4175	6	69 (10–89)
Yes	603	52,311	81	283	30,842	44	−10 (−64; 27)	532	49,676	81	122	14,020	20	−24 (−114; 28)
1 Oct – 31 Dec 2022														
Overall	558	28,037	61	300	14,816	32	29 (−15; 56)	471	25,323	61	115	5328	12	24 (−49; 61)
By infection type														
Asymptomatic	558	28,037	27	300	14,816	11	60 (9–83)	471	25,323	27	115	5328	3	57 (−48; 88)
Symptomatic	558	28,037	34	300	14,816	21	2 (−80; 46)	471	25,323	34	115	5328	9	−4 (−135; 54)
By prior infection														
No	122	5719	17	95	4875	18	31 (−55; 69)	97	5011	17	28	1411	3	53 (−90; 88)
Yes	434	22,000	44	199	9601	14	32 (−28; 64)	373	20,055	44	86	3850	9	0 (−115; 53)
1 Jan – 2 May 2023														
Overall	532	36,205	52	364	28,952	47	−54 (−146; 3)	515	35,472	52	149	13,121	14	−13 (−129; 44)
By infection type														
Asymptomatic	532	36,205	25	364	28,952	27	−52 (−187; 20)	515	35,472	25	149	13,121	8	−55 (−324; 43)
Symptomatic	532	36,205	27	364	28,952	20	−53 (−201; 22)	515	35,472	27	149	13,121	6	11 (−147; 68)
By previous infection														
No	99	5735	15	86	6952	17	−2 (−174; 62)	97	5693	15	29	2764	3	82 (13–96)
Yes	429	30,311	37	271	21,241	30	−66 (−186; 4)	415	29,621	37	118	10,170	11	−71 (−281; 23)

PT = patient time (days); e = events; rVE = relative vaccine effectiveness; CI=Confidence interval.
Fully adjusted: by hospital, age, sex, at least one underlying condition, prior SARS-CoV-2 infection (excepting for the analyses stratified by this variable).

Table 4
Adjusted Hazard ratio of the COVID-19 second booster by outcome and time since second booster dose in the primary analysis, VEBIS HCW study, 1 October 2022–2 May 2023.

Outcome	Dose	Number HCWs	Events	Person time	Fully adjusted rVE rVE% (95 % CI)
Any infection	First booster>3 months	768	113	64,242	ref
	Second booster<3 months	334	41	20,634	3 (−46; 36)
	Second booster≥3 months	331	38	23,134	−15 (−79; 26)
Asymptomatic infection	First booster>3 months	768	52	64,242	ref
	Second booster<3 months	334	16	20,634	32 (−30; 65)
	Second booster≥3 months	331	22	23,134	−12 (−6; 39)
Symptomatic case	First booster>3 months	768	61	64,242	ref
	Second booster<3 months	334	25	20,634	−27 (−116; 25)
	Second booster≥3 months	331	16	23,134	−8 (−107; 44)

Fully adjusted: Adjusted by age, sex, site, underlying conditions, previous infection; rVE = relative vaccine effectiveness; CI = confidence interval.

when multiple ancestral vaccine doses prevent the immune system from responding to newer variants or vaccines compared to less vaccinated persons. For example, in a subset of HCWs in Israel, those with initial low antibody levels remained at increased susceptibility to infection despite a significant boost in neutralising antibody titers after a fourth COVID-19 vaccine dose [23].

The growing body of evidence on COVID-19 VE indicates the vaccines to be less effective against mild outcomes such as infection, and that this effectiveness wanes rather quickly. However, the authorised COVID-19 vaccines remain effective against severe outcomes such as hospitalisation and death, and this protective effect is sustained both over time and across emerging variants [24,25].

This study measured the rVE, which is the added protection of a vaccine dose in addition to the protection provided by previous doses and by past infections. In a generally healthy population such as a HCW cohort, where past infections are common due to high exposure, and where very few individuals would develop severe disease even without vaccination, the effect of additional vaccine doses is lower than absolute VE that has the infection rate in the unvaccinated population as reference. However, due to the potential transmission of infection to vulnerable individuals in this setting and to maintain a strong workforce in the healthcare setting, vaccination of HCW remains a priority in many countries.

Our study has some limitations that need to be taken into account in the interpretation of the results. Firstly, HCWs recruited to the study may not be representative of the wider workforce in hospitals in terms of roles or vaccination uptake. However, the low uptake of the second booster vaccination in participating hospitals was similar to that observed in the study in most of the hospitals. In addition, the VE would be biased towards the null if vaccination was associated with a higher risk of infection due to, for example, staff performing high-risk procedures or exhibit riskier behaviours due to overconfidence in vaccination. Adjusting for the clinical role did not modify the results and had slightly worse fit in the regression model. Secondly, the study was not powered to adjust for other possible confounders, although we collected additional information on different risk and protective factors. Thirdly, anti-N serology tests could not be performed in 3/12 sites, although anti-S serology was performed in all sites. As such, it may be possible that some infections were missed in these sites, although only two infections were missed in the nine sites performing anti-N serology. A differential misclassification of these infections in the three sites between those vaccinated with the second and first booster dose would have underestimated the rVE results. Finally, viral sequencing was performed in some sites, while for the others we relied on the data at the national level. However, in the sites with sequencing performed, these data concurred with the GISAID information. Our results are based on longer follow-up in some hospitals with different variant and sub-lineages circulation. We cannot exclude heterogeneity between the study sites related to the virus circulation timing and to vaccination behaviours. Adjusting by hospital and using calendar time as underlying time in the study could potentially have addressed these aspects. Aside from that, our study presents some important methodological strengths that increase confidence in the results. These are related to the number of hospitals participating in study, the use of regular (weekly or fortnightly) testing, and data collection with high completeness of key variables, including for prior COVID-19 episodes.

In conclusion, the bivalent COVID-19 vaccines may have reduced the risk of SARS-CoV-2 infection compared to the residual protection from the first booster dose by 11 %. HCWs with no prior SARS-CoV-2 infection and those with asymptomatic infection may have benefited more from the second booster of the COVID-19 vaccine during the 2022–2023 season. The update of the COVID-19 vaccine antigen composition has the objective to enhance vaccine-induced immune responses to circulating strains and this in combination with ensuring timely delivery so that protection lasts enough to cover the COVID-19 waves are the most important aspects to be taken into account when designing the future COVID-19 vaccination policies. In this high-risk population, promoting testing when in contact with vulnerable patients, reinforcing the use of protective equipment as well as promotion of hand and respiratory hygiene represent additional protective measures that should always be considered in addition to vaccination. The continued support of HCW cohorts in which regular testing is done provides a powerful platform to monitor and investigate further the effectiveness of COVID-19 vaccines and inform the development of key public health interventions for this population.

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Declaration of competing interest

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If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

The authors do not have permission to share data.

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