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COVID-19 vaccine effectiveness among healthcare workers: a hospital-based cohort study

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ABSTRACT

Objectives Healthcare workers (HCWs) were the first to be prioritised for COVID-19 vaccination. This study aims to estimate the COVID-19 vaccine effectiveness (VE) against SARS-CoV-2 symptomatic infection among HCWs in Portuguese hospitals.

Design Prospective cohort study.

Setting and participants We analysed data from HCWs (all professional categories) from three central hospitals: one in the Lisbon and Tagus Valley region and two in the central region of mainland Portugal, between December 2020 and March 2022. VE against symptomatic SARS-CoV-2 infection was estimated as one minus the confounder adjusted HRs by Cox models considering age group, sex, self-reported chronic disease and occupational exposure to patients diagnosed with COVID-19 as adjustment variables.

Results During the 15 months of follow-up, the 3034 HCWs contributed a total of 3054 person-years at risk, and 581 SARS-CoV-2 events occurred. Most participants were already vaccinated with a booster dose (n=2653, 87%), some are vaccinated with only the primary scheme (n=369, 12.6%) and a few remained unvaccinated (n=12, 0.4%) at the end of the study period. VE against symptomatic infection was 63.6% (95% CI 22.6% to 82.9%) for HCWs vaccinated with two doses and 55.9% (95% CI −1.3% to 80.8%) for HCWs vaccinated with one booster dose. Point estimate VE was higher for individuals with two doses taken between 14 days and 98 days (VE=71.9%; 95% CI 32.3% to 88.3%).

Conclusion This cohort study found a high COVID-19 VE against symptomatic SARS-CoV-2 infection in Portuguese HCWs after vaccination with one booster dose, even after Omicron variant occurrence. The small sample size, the high vaccine coverage, the very low number of unvaccinated individuals and the few events observed during the study period contributed to the low precision of the estimates.

INTRODUCTION

The COVID-19 pandemic has been an ongoing Public Health Emergency of International Concern since December 2019. As of week 2022–12, the European Union/European Economic Area (EU/EEA) countries had reported 125 484 993 cases and 1055 344 deaths, of which 2.8% cases (n=3564 977) and 2.1% deaths (n=21 637) were reported in Portugal.[1]

After the implementation of unprecedented non-pharmacological public health measures, including confinement orders in many countries, COVID-19 vaccines were developed and made available. Since then, vaccination has proved to be an essential tool to reduce transmission of SARS-CoV-2, as well as severe illness and COVID-19-related mortality.[2]

Healthcare workers (HCWs) are essential to ensure healthcare for patients in a pandemic context.[3 4] HCWs were among the first prioritised for COVID-19 vaccination as they are at increased risk for exposure to SARS-CoV-2 due to their close contact with patients with COVID-19. Additionally, HCWs can transmit the infection to susceptible patients at high risk of severe COVID-19. According to the Portuguese vaccination plan, vaccination of HCWs started on 27 December 2020, primarily with the mRNA vaccine (Comirnaty) and AdV vaccine Vaxzevria (AstraZeneca).[5]

Despite the high efficacy of these vaccines, many factors can affect their performance in a real world situation, outside the strict setting

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is one of the first studies to estimate vaccine effectiveness in healthcare workers (HCWs), including during the Omicron variant phase.

⇒ The relatively small sample size of the HCW cohort (n=3034), the high vaccine coverage (87%), the very low number of unvaccinated individuals and the few events observed during the study period (n=581) contributed to the low precision of the estimates.

⇒ The number of events may be underestimated because some positive cases could be diagnosed outside of the hospital context

of clinical trials, which supports the importance of observational studies to assess vaccine effectiveness (VE).[6] Most observational studies initially described high VE for available vaccines. However, VE was expected to decrease over time both due to the emergence of new variants, namely the Omicron variant, and the waning of protection.[7–9]

Results from cohort studies conducted in the USA, Denmark and Italy estimated that VE for the primary vaccination scheme was above 80% for the alpha predominant period and 70% for the delta, among HCWs.[10–14] However, these studies reported short follow-up periods. More extended follow-up studies among HCWs are still limited, especially regarding the period of the Omicron variant predominance. Other studies focusing on VE against the Omicron variant have presented lower estimates for the general public against primary course and booster vaccines delta.[15–17] In Malaysia, a study using electronic recordsfound marginally smaller effectiveness of the booster against infection in the Omicron period (40–50 percentage points) compared with the Delta; varying between 30.14 (28.39, 31.84) and 51.08 (50.29, 51.87), depending on different vaccine schemes delta.[16] Although studies have assessed different postvaccination time points, results indicated that protection against the Omicron variant waned over time for the booster shot, independently of the vaccination schemes (either heterologous or homologous).[15–17] One study in California, USA, estimated a VE of the three doses against emergency hospital admission of 77% (72%–81%) at less than 3 months and 53% (36%–66%) at 3 months.[15] The same was observed in the UK, where a study found that different vaccine primary course recipients presented increased VE after the booster shot against symptomatic disease at 2–4 weeks, and VE decreased below 65% at 5–9 weeks and below 46% at 10 or more weeks.[17]

This study aims to estimate the COVID-19 VE among hospital HCWs against symptomatic disease in Portugal between December 2020 and March 2022.

METHODS
Study design and population
We developed a cohort study (with retrospectively collected information regarding vaccination and previous infection) that targeted hospital HCWs (all professional categories), eligible for vaccination against COVID-19, without contraindications, and who consented to participate. HCWs were recruited from three different hospitals: one in the Lisbon and Tagus Valley region (Centro Hospitalar Lisboa Ocidental) and two in the Centre region of Portugal (Centro Hospitalar Tondela-Viseu and Centro Hospitalar e Universitário de Coimbra). As the HCW follow-up period started only on 1 June 2021, retrospective data were obtained to cover the period before 1 June 2021 and the total study period was between 27 December 2020 and 31 March 2022. Only HCWs with complete information regarding their vaccination status

(non-vaccination, first dose and second dose, and booster data) were included.

Procedures and collected information
All procedures implemented in this cohort study were based on the Guidance Document 'Cohort study to measure COVID-19 VE among health workers in the WHO European Region'.[16] All HCWs were invited to participate by an email sent by the occupational health service of each hospital. After accepting to participate and signing a written consent form, each HCW answered an enrolment questionnaire implemented in the REDcap platform.[17] Recruitment information included sociodemographics, health status, vaccination history, previous SARS-CoV-2 infection, occupational and community exposure, and preventive behaviours. Self-reported individual COVID-19 vaccination status was also confirmed by the occupational health service of each hospital. Further, every week, participants answered a follow-up questionnaire (through the REDcap platform) which included questions on symptoms and COVID-19 testing in the previous 7 days. The active follow-up started in June 2021, but information regarding reverse transcription PCR (RT-PCR) testing was retrospectively obtained from all participants by the occupational health service of each hospital (from 27 December 2020, the date on which vaccination started, until the end of the study period on 31 January 2022). Each week, RT-PCR testing was performed in hospitals whenever an HCW reported any symptom compatible with COVID-19.

Exposure and outcome definitions
An individual was considered unvaccinated if he/she did not receive any dose of the COVID-19 vaccine. An individual was considered vaccinated 14 days after complete vaccination (receiving all doses recommended in the product characteristics). An individual was considered partially vaccinated 14 days after receiving the first dose and until 14 days after receiving the second dose of the two-dose vaccine. An HCW was considered vaccinated with the booster dose 14 days after receiving this dose. The information for the primary vaccination scheme was retrieved retrospectively in the registries of the occupational health service, since the vaccination of healthcare professionals had already started when the study was implemented.

The outcome of the study was defined as an event of laboratory confirmatory RT-PCR of symptomatic SARS-CoV-2 infection giving the ECDC (European Centre for Disease Prevention and Control) suspected case definition of COVID-19: the presence of at least one of five symptoms (cough, fever, shortness of breath/dyspnoea, anosmia or ageusia/dysgeusia).[18]

Occupational exposure to patients diagnosed with COVID-19 was defined as working in wards with contacts with COVID-19 cases.

Statistical analysis
Participants' characteristics at baseline were described according to the vaccination status (unvaccinated,

partially vaccinated (one dose), fully vaccinated (two doses), booster vaccinated (three doses)). We estimated the COVID-19 symptomatic infection rates per 1000 person-years for each level of vaccination exposure. VE was computed as one minus the confounder-adjusted HR for symptomatic infection, estimated by time-dependent Cox regression[19] with time-dependent vaccine exposure, adjusted for confounding using 7-day periods as strata, as previously published.[20] Additionally, age group (18–35 years/36–50 years/51–70 years), sex (male/female), self-reported chronic disease (yes/no) and occupational exposure to patients diagnosed with COVID-19 (yes/no) were also considered as confounding factors. To assess the sensitivity of the analysis to the inclusion of HCWs with previous infection we also fitted the Cox regression model after the exclusion of previously infected HCWs. Statistical analysis was performed in R V.4.0.5 (R Foundation, Vienna, Austria).

Patient and public involvement
It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research

RESULTS
Participants' characterisation
A comparison of the participant (n=3034) and non-participant HCWs who accepted to respond to a non-participant questionnaire (n=30) is presented in online supplemental table S1. No statistically significant differences were found regarding all of the analysed characteristics, including age group, sex, chronic disease and vaccination status (online supplemental table S1).

Among the 3034 participants, 80.4% (n=2438) were female, 44.4% (n=1347) were aged between 36 years and 50 years, 29.5% (n=585) declared to have at least one chronic disease and 14.8% (n=282) reported working directly with patients with COVID-19 (table 1). No statistically significant differences were found between age group, sex, chronic disease or occupational exposure between vaccinated groups (partially, two doses and booster dose). Most participants were already vaccinated with a booster dose (n=2653, 87%) and only a few remained unvaccinated (n=12, 0.4%) at the end of the study period.

Evolution of vaccination status and events over the study period
The majority of the HCWs were fully vaccinated (two doses) during the first trimester of 2021 (figure 1). Most were vaccinated with the Comirnaty (n=2351) and Vaxzevria (n=665) vaccines (Spikevax vaccine uptake was residual, n=6).

Regarding the booster dose uptake, HCWs were mainly vaccinated in the last trimester of 2021 (starting date 22 October 2021) with the Comirnaty vaccine (n=2563) (data not presented in figure 1).
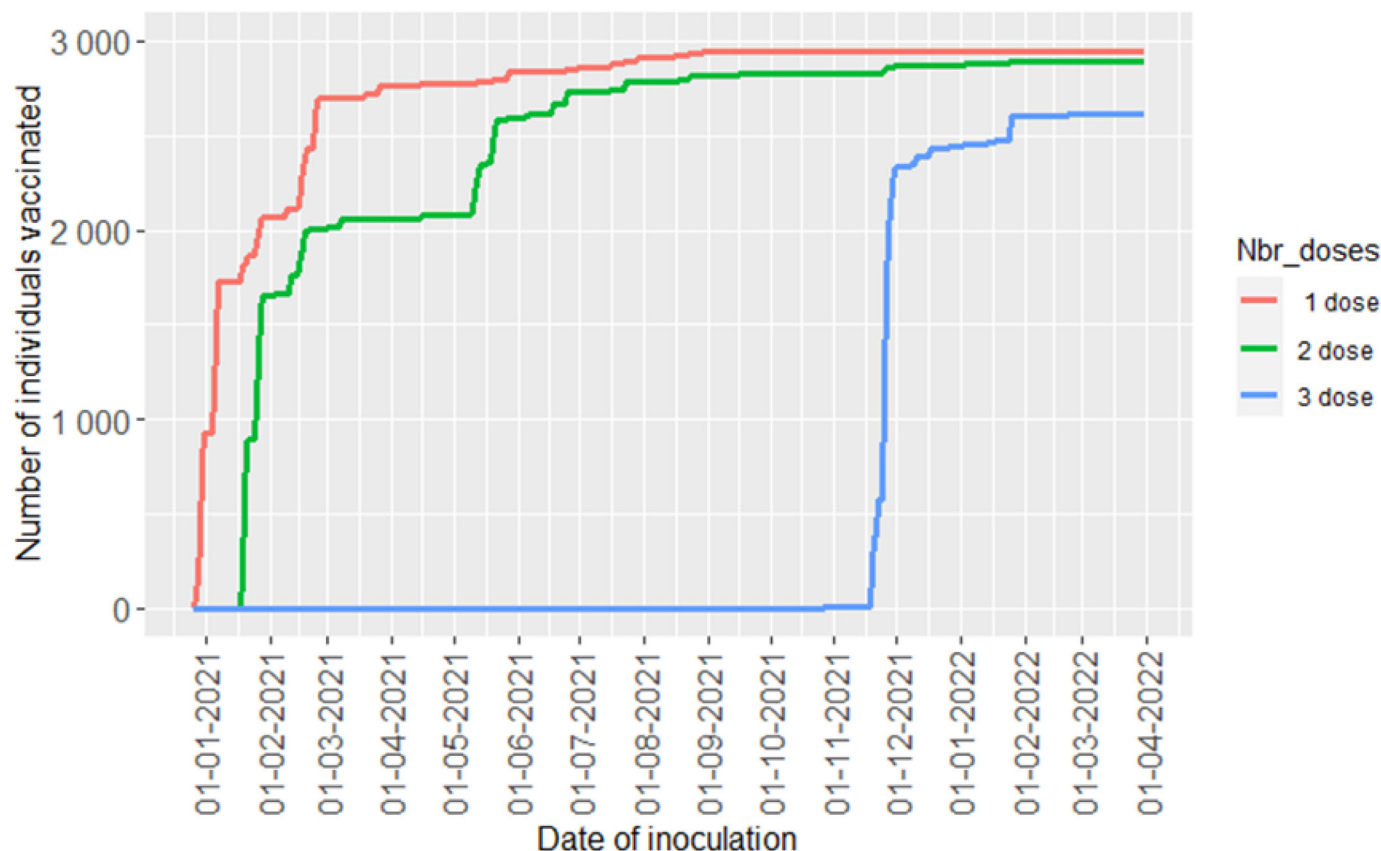
Most SARS-COV-2 infection cases (positive RT-PCR symptomatic cases) occurred at the beginning (January 2021) and at the end (March 2022) of the study period, which coincided with the third and fifth waves of the epidemic in Portugal, respectively (figure 2). A total of 581 events were detected.

VE against symptomatic COVID-19
VE against symptomatic infection was 63.6% (95% CI 22.6% to 82.9%) for HCWs vaccinated with two doses and 55.9% (95% CI −1.3% to 80.8%) for HCWs vaccinated with one booster dose (table 2). Particularly for the individuals vaccinated with two doses we also observed different VE according to the period of follow-up. Although with overlapping CI point estimate VE was

Table 1 General characteristics of the participants, according to their vaccination status

Characteristics	Total (n=3034) n (%)	Unvaccinated (n=12) n (%)	Partially vaccinated (n=58) n (%)	Vaccinated two doses (n=311) n (%)	Vaccinated booster dose (n=2653) n (%)
Age group, years (n=3034)					
18–35	706 (23.3)	1 (8.3)	16 (27.6)	96 (30.9)	593 (22.4)
36–50	1347 (44.4)	9 (75.0)	28 (48.3)	155 (49.8)	1155 (43.5)
51–70	981 (32.3)	2 (16.7)	14 (24.1)	60 (19.3)	905 (34.1)
Sex (n=3034)					
Female	2438 (80.4)	10 (83.3)	49 (84.5)	257 (82.6)	2122 (80.0)
Male	596 (19.6)	2 (16.7	9 (15.5)	54 (17.4)	531 (20.0)
Chronic disease* (n=1982)	585 (29.5)	–	11 (31.4)	48 (27.1)	526 (29.8)
Occupational exposure† (n=1910)	282 (14.8)	–	3 (8.6)	24 (14.5)	255 (14.9)

Differences between groups were assessed using the Pearson's χ^2 test (p<0.05).
*At least one chronic disease.
†Occupational exposure to patients diagnosed with COVID-19.

Figure 1 Evolution of primary vaccination status of the participants over the study period (Participants who reported taking the Spikevax vaccine (n=6) are not represented in this figure. For heterologous vaccination (n=109), the vaccine brand first was defined as the first dose brand).

higher for individuals with two doses taken between 14 days and 98 days (VE=71.9%; 95% CI 32.3% to 88.3%).

When we restricted our sample to the HCWs not previously infected (n=2960), similar results were obtained (see online supplemental table S2).

DISCUSSION

Our study suggests high levels of protection against symptomatic SARS-CoV-2 infection in Portuguese HCWs, conferred by full vaccination schemes of Comirnaty and Vaxzevria and additional Comirnaty booster dose. To our knowledge, this is one of the first studies to estimate VE in HCWs, including during the Omicron variant phase. A similar cohort study, still in preprint, also performed in HCWs from the USA, found an estimate of VE (82.3%, 95% CI 75.1% to 87.4%) considering the period between December 2020 and September 2021.[21] Other studies of HCWs have already been published but they mostly referred to a period in time not comparable to the present study (before Omicron variant predominance) and estimates tend to be higher (above 80%) than the estimate obtained in the present study.[13–15] Point estimate VE was higher in the first 3 months after full vaccination of primary schedule, which may be related to alpha/delta predominance and lower waning immunity.[9] However, the lower number of events did not enable us to assess

statistically significant differences when compared with ≥98 days after the second dose.

Our study has some limitations and possible sources of bias. One is related to the sample size and the small number of unvaccinated individuals. The relatively small sample size of the HCWs cohort (n=3034), the high vaccine coverage and the few events observed during the study period contributed to the low precision of the estimates and precluded to estimate VE according to the brand of vaccine or other individual HCW characteristics. Moreover, most of the events occurred in restricted periods (beginning and end of the study period) while no events were observed in most of the follow-up weeks. However, the distribution of events over time was comparable to the epidemic curve observed in the Portuguese community aged between 18 years and 70 years for the same period.[22] Additionally, we may be failing to detect all the events that occurred during the study period because some positive cases could be diagnosed outside of the hospital context, which may impact VE. Nevertheless, we tried to minimise this information bias through the weekly follow-up questionnaire asking participants if they were testing outside the hospital. In the case of outside testing, result and testing data were obtained by self-reporting and these positive cases were also considered valid events.
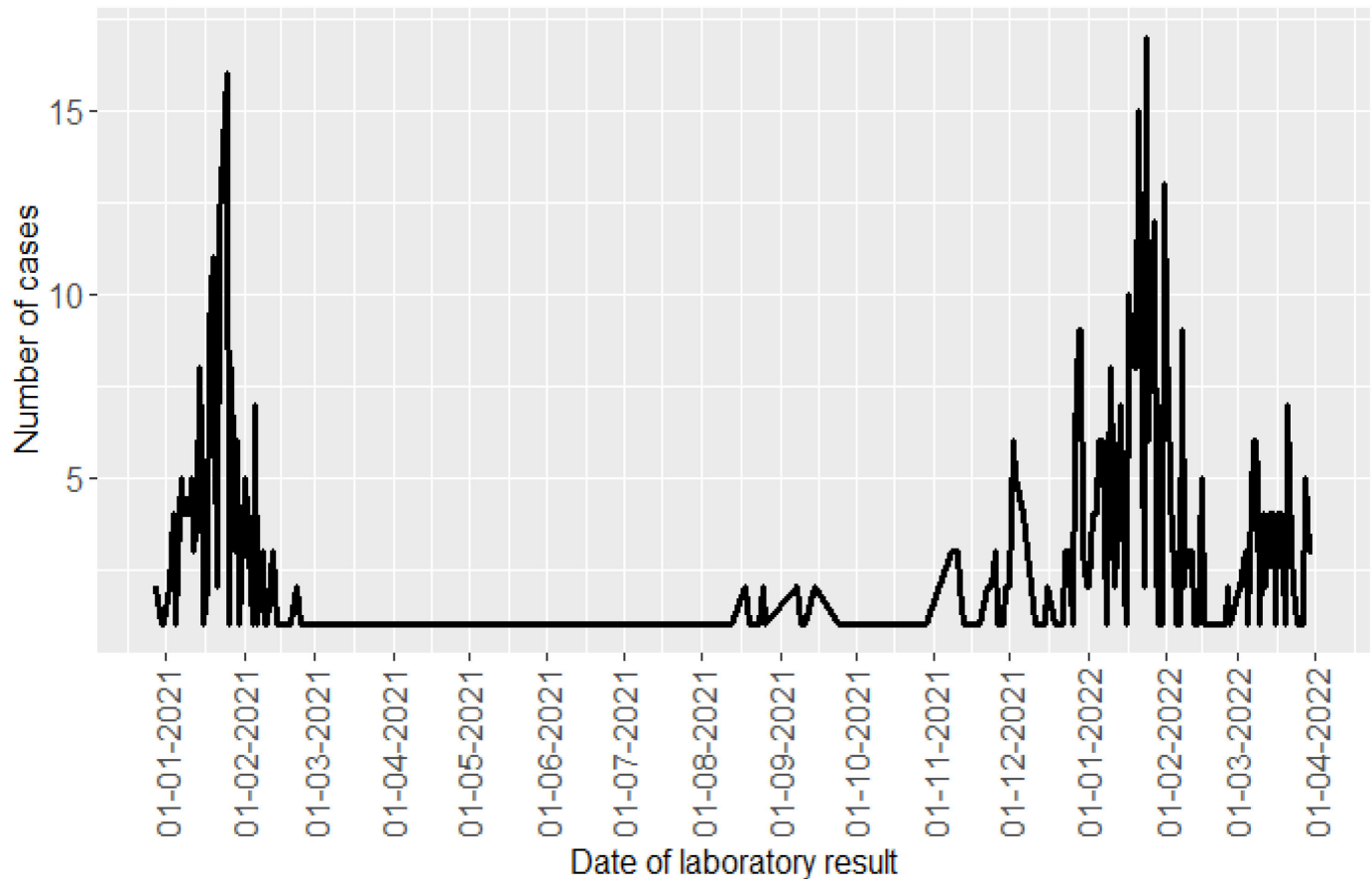
Figure 2 Evolution of the events (positive RT-PCR symptomatic cases) during the study period.

Table 2 VE against symptomatic COVID-19

Vaccine status	Person-years	Events (n)	Rate*	Confounder-adjusted HR (95% CI)†	VE (95% CI)
Unvaccinated	255	103	404.2	Reference	Reference
Unvaccinated (V1_0:13)‡§	104	34	328.5	–	–
Partially (v1_14⁺v2-14)‡¶	339	36	106.3	–	–
Vaccinated with two doses (v2_14⁺)**	2024	99	48.9	0.36 (0.17 to 0.77)	63.6 (22.6 to 82.9)
Vaccinated with two doses (v2_14–98)††	644	13	20.2	0.28 (0.12 to 0.68)	71.9 (32.3 to 88.3)
Vaccinated with two doses (v2_98⁺)‡‡	1380	86	62.3	0.54 (0.21 to 1.44)	45.6 (-44.2 to 79.5)
Vaccinated with booster (v3_0:13)‡§§	90	26	289.4	–	–
Vaccinated with booster (v3_14⁺)¶¶	708	283	399.9	0.44 (0.19 to 1.01)	55.9 (-1.3 to 80.8)
Total	3520	581	–	–	–

*COVID-19-infection rates per 1000 person-years.
†Confounders: age group, sex, chronic and occupational exposure.
‡HRs and VEs were not calculated for this interim vaccination category due to the small number of events and person-years.
§Vaccinated with two doses ≥14 days ago.
¶Vaccinated with one dose ≥14 days ago and with second dose <14 days ago.
**Vaccinated with two doses ≥14 days ago
††Vaccinated with two doses ≥14 days ago and <98 days.
‡‡Vaccinated with two doses ≥98 days ago.
§§Vaccinated with booster dose <14 days ago.
¶¶Vaccinated with booster dose <14 days ago.
VE, vaccine effectiveness.

Participant HCWs could not have adequately represented the overall HCWs in the studied hospitals. Despite the low number of non-participant questionnaires (n=30), the two groups of HCWs were similar regarding age group, sex, chronic disease prevalence and vaccination status. Additionally, due to the high coverage of vaccination in the participating hospitals (>90%), the possibility that the non-vaccinated HCWs might have been less motivated to participate or to be followed up is also negligible.

The inclusion of HCWs with a previous infection could also be a source of bias. However, when we performed a sensitivity analysis after excluding HCWs previously infected, similar results were obtained.

Finally, this study did not include variables related to adherence to other preventive behaviours or other individual characteristics that may be associated with either vaccination uptake or risk of infection. Nonetheless, the high coverage rate of COVID-19 vaccine uptake among HCWs does not suggest the impact of individual characteristics.

Larger cohort studies of HCWs with long follow-up periods relied on reporting of weekly symptoms, but this posed a high burden making it difficult to maintain for participants. One possible solution to obtain more robust VE estimates in this risk group is to use cohorts based on electronic registries as previously performed for other risk groups in Portugal.[20] The present work did not use electronic registries because electronic registries also pose some limitations, namely in obtaining important adjustment data in the hospital context, such as occupational exposures. Moreover, it would imply the full identification of HCWs within the databases, something that is not yet operationalised.

Conclusion

This cohort study suggests high VE for COVID-19 against symptomatic SARS-CoV-2 infection in Portuguese HCWs, after vaccination with a booster dose, and even after the Omicron variant occurrence. The small sample size, the high vaccine coverage, the very low number of unvaccinated individuals and the few events observed during the study period contributed to the low precision of the estimates.

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval Written informed consent was obtained from all study participants after being informed that participation was voluntary and that he/she could withdraw from the study at any time without justification or consequences, particularly about the offer of vaccination. All data were anonymised before statistical analysis by the occupational health services of each hospital. The study protocol was approved by the ethics committee of the Instituto Nacional de Saúde Doutor Ricardo Jorge (date of approval: 16 April 2021) and by the ethics committees of the two participating hospitals, namely by the ethics committee ofCentro Hospitalar Tondela-Viseu (CHTV) (Ref.06/16/04/2021, date of approval 16 April 2021) and Centro Hospitalar Lisboa Ocidental (CHLO) (Ref. 2141, date of approval 19 May 2021).

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