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The effectiveness of mRNA vaccines to prevent SARS-CoV-2 infection and hospitalisation for COVID-19 according to the time elapsed since their administration in health professionals in the Valencian Autonomous Community (Spain)

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ABSTRACT

The objective was to understand the effectiveness of the BNT162b2 and mRNA-1273 vaccines against SARS-CoV-2 in health professionals(HPs) in the Valencian Autonomous Community(Spain) who had completed a full vaccination regimen, both in terms of preventing infections and avoiding hospitalisations, according to the time elapsed since the vaccine administration.

Case-controlled study with negative test results. HPs who had undergone at least one PCR or antigen(Ag) active infection diagnostic test(AIDT) to rule out SARS-CoV-2 infection between 25 January and 18 July 2021 were included. HPs with positive AIDT result were considered as cases and those with a negative result controls. Adjusted vaccine effectiveness(VEa) to prevent SARS-CoV-2 infection and its 95% confidence interval(95% CI) were calculated using the formula $VEa = (1 - OR) \times 100$.

The VEa for the prevention of SARS-CoV-2 infection 12 to 120 days after completing the full two-dose vaccine regimen was 91.6%(95%CI[89.6%,93.2%]) for the BNT162b2 vaccine and 95.2%(95%CI[88.3%,98.1%]) for the mRNA-1273 vaccine. After 120 days the VEa was 71.5%(95%CI[67.0%,75.5%]) for the BNT162b2 vaccine and 88.3%(95%CI[75.7,94.4%]) for the mRNA-1273 vaccine. The VEa for prevention of hospitalisation for COVID-19 for the complete two-dose regimen of mRNA vaccines (BNT162b2 and mRNA-1273) was 96.8%(95%CI [76.1%,99.6%]).

The administration of the complete regimen of the BNT162b2 and mRNA-1273 vaccine against SARS-CoV-2 was highly effective for the prevention of COVID-19 cases in HPs when 12 to 120 days had elapsed since the second dose. However, said effectiveness decreased as time from the vaccine administration elapsed, although it was maintained for the prevention of hospitalisation of HPs.

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1. Introduction

The coronavirus disease (COVID-19) caused by SARS-CoV-2 has affected >424 million people and has caused >5.8 million deaths worldwide (Johns Hopkins University Coronavirus Resource Center, 2020). The measures used to reduce the transmission of SARS-CoV-2 were insufficient to control the pandemic and at the end of 2020 the appearance of the first vaccines against SARS-CoV-2 infection came to constitute a turning point the control of the disease. In Spain, this was complemented by implementation of actions by the autonomous communities designed to prevent the appearance of the disease and reduce its severity and mortality, especially by prioritising the impact of the pandemic on the national health system (European Centre for Disease Prevention and Control, 2020a; European Centre for Disease Prevention and Control, 2020b; Estrategia de vacunación COVID-19 en España líneas maestras, 2020; Estrategia de vacunación frente a COVID-19 en España, 2022).

In Spain, as in the rest of the European Union, vaccination against COVID-19 established priority groups from among the general population, as stated in the Spanish COVID-19 Vaccination Strategy, which is continuously reviewed and updated (European Centre for Disease Prevention and Control, 2020a; European Centre for Disease Prevention and Control, 2020b). The first phase included the residents and social and healthcare personnel working at residences for elderly and disabled people, as well as frontline health professionals (HPs). Following, the European Commission authorised two messenger RNA (mRNA) vaccines were available when the vaccination program started in HPs: BNT162b2 (Comirnaty®-Pfizer/BioNTech®) and Spikevax®, previously known as COVID-19-Vaccine-Moderna®.

In Spain, >39 million people have now received at least one dose of the vaccine (representing 92.9% of the population aged over 12 years) and almost 39 million have received a complete two-dose vaccination regimen (representing 92.4% of the Spanish population aged over 12 years) (Ministerio de Sanidad, 2022). Furthermore, >10 million doses have been administered worldwide (Johns Hopkins University Coronavirus Resource Center, 2020). The data available for the different mRNA vaccines show vaccine efficacy (VE) figures exceeding 90%, with the VE of the BNT162b2 vaccine being close to 100% in paediatric age groups, although studies have established that the true efficacy could range between 75% and 100% (Polack et al., 2020; Baden et al., 2021). Nonetheless, outside of clinical trial protocols, several factors can affect the effectiveness of vaccines, including their storage conditions, distribution, reconstitution or administration, different comorbidities and pathologies of patients receiving them, time elapsed from the vaccine administration, and characteristics of the predominant variant circulating at the time of infection (European Centre for Disease Prevention and Control, 2022). Thus, effectiveness studies must be implemented to assess whether these vaccines offer the same protection in real world conditions, both for the prevention of infection and serious disease, and to assess whether their effectiveness changes depending on the time elapsed since their administration.

In this sense, the European Medicines Agency (EMA) and the European Centre for Disease Prevention and Control (ECDC) have indicated that our knowledge of the behaviour of vaccines outside of clinical trials must be increased. Such studies will be key to generating evidence evaluating the continued benefits and risks of vaccines and can help inform decision-making about their use, both in national vaccination strategies and in different populations, including HPs (European Centre for Disease Prevention and Control, 2021). Various studies evaluating the effectiveness of these vaccines have been published and complement the initial VE results with varying estimates according to the individual study population and objectives (Dagan et al., 2021; Thompson et al., 2021; Keehner et al., 2021; Skowronski and De Serres, 2021). Not only the direct protection conferred by the first doses of vaccination are important to consider, but also the indirect protection achieved when a large proportion of population is immunized, providing a reduction in SARS-CoV-2 circulation. Several studies highlight the importance of the decrease in SARS-CoV-2 circulation in persons who have received a single dose and in those who are fully vaccinated, showing a VE of 86% (95% CI: 76–97%) for SARS-CoV-2 infection prevention in fully vaccinated persons. Furthermore, this extensive vaccine application between the first and second dose has also reduced virus circulation within hospitals conferring a reduced risk of healthcare-associated outbreaks and infections among healthcare workers (Liu et al., 2021; Stefanizzi et al., 2021).

In our region, the Autonomous Valencian Community created the Valencian COVID-19 Vaccine Research Program (ProVaVac) (DECRETO 10/2021, de 16 de marzo, del President de la Generalitat por el que se crea el Comité Científico del Programa Valenciano de Investigación Vacunal COVID-19 (ProVaVac), 2021) with the aim of evaluating VE in the HPs in its territorial area.

Given all the above, the objective of this current work was to understand the effectiveness of the BNT162b2 and mRNA-1273 vaccines against SARS-CoV-2 in HPs in the Valencian Autonomous Community, after having completed the full two-dose vaccine regimen, both in terms of the prevention of infection and of hospitalisation, according to the time elapsed since their administration.

2. Methods

We conducted a case-controlled study with negative test results in HPs with a contractual relationship with the Ministry of Universal Health and Public Health between 1 January and 29 May 2021. The study period ran from epidemiological week (EW) 4 in 2021 (starting on 25 January) to EW 28 in 2021 (ending on 18 July). The vaccination campaign against SARS-CoV-2 aimed at HPs began on 8 January 2021 with the BNT162b2 and mRNA-1273 vaccines, following the reconstitution and administration recommendations from the corresponding technical data sheets (Guía Técnica COMIRNATY (Vacuna COVID-19 ARNm, Pfizer-BioNTech), 2022; Guía Técnica SPIKEVAX (Vacuna COVID-19 ARNm, Moderna), 2022). HPs who had undergone at least one PCR or antigen (Ag) active infection diagnostic test (AIDT) during the study period were included in this current work. HPs with a positive AIDT result were considered a case, while those with negative AIDT results were used as controls.

Data was collected according to the ProVaVac study protocol, starting by extracting data via the Health Information Systems Analysis Service of the Ministry of Universal Health and Public Health. The date of birth, sex, health department affiliation, work centre, professional category, and specialty were obtained for each of the HPs from the human resources database. The results of AIDTs carried out between 25 January and 18 July 2021 were obtained from the Valencian Community Microbiological Surveillance Network (RedMIVA in its Spanish acronym) database which records the results of the microbiology laboratory tests conducted at all the health centres in the Valencian Community. Vaccination status was collected from the Nominal Vaccination Registry (RVN in its Spanish initialism). The RVN is a database containing all the records of the vaccines administered to each citizen receiving healthcare in the Valencian Autonomous Community. The type of vaccine and date of administration of the first and second dose was retrieved for each HP. The different comorbidities and active diagnoses were obtained from the Alumbra database which integrates the information systems of every health department and allows exploitation of clinical data.

HPs were considered fully vaccinated if they had received the second vaccine dose at least 12 days before the AIDT. Those in which 12 to 120 days had elapsed between the administration of the second dose and the date of the AIDT were classified in the 12–120 group. HPs were classified in the >120 group if >120 days had elapsed between the administration of the second dose and the date of the AIDT. Finally, HPs with no SARS-CoV-2 vaccine doses registered in the RVN were considered unvaccinated. The study was approved by the Drug Research Ethics Committee

at the Alicante-Hospital General Department of Health, with protocol number PI2021–079.

2.1. Data analysis

Firstly, the characteristics of all the HPs included in the study were described according to their SARS-CoV-2 vaccination status and time elapsed since the administration of the vaccine. The different groups were then compared using chi-squared tests. Next, to study the association between SARS-CoV-2 infection and vaccination status and the other variables (age, sex, professional category, professional setting, and different comorbidities), the unadjusted odds ratio (OR) and adjusted odds ratio (ORa) were calculated using a logistic regression model. Variables with statistically significant differences between the different vaccination groups (based on the time elapsed post-vaccination) and the vaccine administered, as well as those significantly associated with the development of a SARS-CoV-2 infection were introduced into the regression model. Likewise, the OR and ORa were also calculated using a logistic regression model to study the association between hospitalisation for COVID-19 and vaccination status or the other variables (age,

Table 1
Characteristics of the health professionals included in this study according to the vaccination regimen they had received ($n = 6364$).

	Total *n* (%)	Complete regimen *n* (%)	Pfizer	Pfizer	Moderna	Moderna	Unvaccinated *n* (%)	p_1	p_2
			Complete 12–120 days *n* (%)	Complete > 120 days *n* (%)	Complete 12–120 days *n* (%)	Complete > 120 days *n* (%)			
Total	6364 (100)	3911 (61.5)	1820 (19.9)	1843 (20.1)	149 (1.6)	99 (1.1)	2453 (26.8)		
Sex								0.064	0.200
Male	1504 (23.6)	955 (24.4)	453 (24.9)	438 (23.8)	41 (27.5)	23 (23.2)	549 (22.4)		
Female	4860 (76.4)	2956 (75.6)	1367 (75.1)	1405 (76.2)	108 (72.5)	76 (76.8)	1904 (77.6)		
Age								0.190	< 0.001
≤ 39	2754 (43.3)	1697 (43.4)	800 (44.0)	820 (44.5)	44 (29.5)	33 (33.3)	1057 (43.1)		
40–59	2774 (43.6)	1679 (42.9)	756 (41.5)	798 (43.3)	73 (49.0)	52 (52.5)	1095 (44.6)		
≥ 60	836 (13.1)	535 (13.7)	264 (14.5)	225 (12.2)	32 (21.5)	14 (14.1)	301 (12.3)		
Professional category								< 0.001	< 0.001
Medical practice	1598 (25.1)	1163 (29.7)	476 (26.2)	633 (34.3)	29 (19.5)	25 (25.3)	435 (17.7)		
Nursing	2078 (32.7)	1294 (33.1)	615 (33.8)	609 (33.0)	40 (26.8)	30 (30.3)	784 (32.0)		
Auxiliary staff/technicians	1528 (24.0)	835 (21.4)	406 (22.3)	357 (19.4)	44 (29.5)	28 (28.3)	693 (28.3)		
Others[a]	1160 (18.2)	619 (15.8)	323 (17.7)	244 (13.2)	36 (24.2)	16 (16.2)	541 (22.1)		
Professional setting								< 0.001	< 0.001
Primary healthcare services	1415 (22.2)	958 (24.5)	419 (23.0)	532 (28.9)	4 (2.7)	3 (3.0)	457 (18.6)		
Specialised area/others[b]	4949 (77.8)	2953 (75.5)	1401 (77.0)	1311 (71.1)	145 (97.3)	96 (97.0)	1996 (81.4)		
Comorbidities									
Asthma	569 (8.9)	352 (9.0)	167 (9.2)	171 (9.3)	6 (4.0)	8 (8.1)	217 (8.8)	0.834	0.296
Cancer	268 (4.2)	179 (4.6)	95 (5.2)	70 (3.8)	11 (7.4)	3 (3.0)	89 (3.6)	0.067	0.022
Cerebrovascular disease	81 (1.3)	50 (1.3)	25 (1.4)	24 (1.3)	1 (0.7)	0 (0.0)	31 (1.3)	0.959	0.760
Diabetes	277 (4.4)	186 (4.8)	94 (5.2)	78 (4.2)	12 (8.1)	2 (2.0)	91 (3.7)	0.047	0.021
Chronic obstructive pulmonary disease	95 (1.5)	61 (1.6)	33 (1.8)	23 (1.2)	3 (2.0)	2 (2.0)	34 (1.4)	0.578	0.614
Liver disease	256 (4.0)	164 (4.2)	86 (4.7)	64 (3.5)	11 (7.4)	3 (3.0)	92 (3.8)	0.382	0.065
Immunosuppression	21 (0.3)	14 (0.4)	8 (0.4)	5 (0.3)	0 (0.0)	1 (1.0)	7 (0.3)	0.623	0.576
Obesity	549 (8.6)	329 (8.4)	173 (9.5)	138 (7.5)	14 (9.4)	4 (4.0)	220 (9.0)	0.442	0.094
Other respiratory diseases	32 (0.5)	23 (0.6)	15 (0.8)	7 (0.4)	0 (0.0)	1 (1.0)	9 (0.4)	0.225	0.166
Chronic renal disease	94 (1.5)	60 (1.5)	32 (1.8)	18 (1.0)	7 (4.7)	3 (3.0)	34 (1.4)	0.634	0.002
Tobacco use	611 (9.6)	361 (9.2)	162 (8.9)	169 (9.2)	17 (11.4)	13 (13.1)	250 (10.2)	0.205	0.356
Thalassemia	40 (0.6)	25 (0.6)	14 (0.8)	9 (0.5)	2 (1.3)	0 (0.0)	15 (0.6)	0.892	0.556
Transplant recipient	9 (0.1)	5 (0.1)	3 (0.2)	2 (0.1)	0 (0.0)	0 (0.0)	4 (0.2)	0.741	0.958

p_1: The p value of the comparison between health professionals that had completed the vaccination regimen versus those who were unvaccinated.
p_2: The p value of the comparison between health professionals that had received different vaccination regimens as a function of time versus those who were unvaccinated.

[a] Guards, administrative staff, and maintenance staff.
[b] Municipal Emergency Assistance Service (SAMU), central services, general directorates, public health centres, and departmental management units.

sex, professional category, professional setting, and different comorbidities). Finally, the adjusted vaccine effectiveness (VEa) with its 95% confidence interval (95% CI) was calculated for the different vaccination regimens, both for the prevention of SARS-CoV-2 infection and of hospitalisation, using the formula VEa = (1 − ORa) × 100. The level of statistical significance was set to $p < 0.05$ and the analysis was performed using SPSS software (version 25.0; IBM Corp., Armonk, NY).

3. Results

Of the 69,865 HPs who maintained a contractual relationship with the Autonomous Valencian Community, there were no registered AIDTs for 86.9% (60,700) of them, while 13.1% (9165) had undergone at least one AIDT. Of these, 251 HPs were excluded (33 because they had received the Janssen vaccine and 218 because they had received the AstraZeneca vaccine), leaving a total of 8914 HPs. We retained those who had received a full two-dose vaccine regimen or who were unvaccinated (excluding those who had received only one vaccine dose), leaving a total of 6364 HPs. Of these, 3911 had received the full vaccine regimen (3663 with Pfizer and 248 with Moderna) and 2453 were completely unvaccinated; 76.4% (4860) were women and 43.6% (2774) were aged between 40 and 59 years. A total of 1820 (19.9%) on the Pfizer regimen and 149 (1.6%) on the Moderna regimen were considered vaccinated with the complete two-dose regimen, with 12 to 120 days having elapsed since the administration.

There were statistically significant differences in age, professional category, and professional setting ($p < 0.001$), as well as in diabetes, cancer, and chronic kidney disease among the different groups created according to the time elapsed since vaccine administration. The remaining patient characteristics studied are shown in Table 1 according to their vaccination status. A total of 1469 HPs (23.1%) were considered a COVID-19 case and 4895 (76.9%) were considered controls. The frequency of SARS-CoV-2 infection after 12 to 120 days had elapsed since completion of the full Pfizer two-dose vaccination regimen was 35.0% in the controls versus 7.3% in the cases ($p < 0.001$) while it was 31.0% in the controls versus 22.3% in the cases ($p < 0.001$) when >120 days had elapsed since its administration (Table 2).

The VEa for the prevention of SARS-CoV-2 infection 12 to 120 days after administration of the complete regimen of two Pfizer vaccine doses was 91.6% (95% CI [89.6%, 93.2%]), or 71.5% (95% CI [67.0%, 75.5%]) when >120 days had elapsed. The VEa for the prevention of SARS-CoV-2 infection of the complete two-dose Moderna vaccine regimen was 95.2% (95% CI [88.3%, 98.1%]) when 12 to 120 days had elapsed since its administration, and was 88.3% (95% CI [75.7%, 94.4%]) when >120 days had passed. The VEa for each of the rest of the subgroups is shown in Table 3. The frequency of hospital admissions for COVID-19 after completion of the full vaccine regimen was 4.8%, compared to 61.6% in patients admitted for another reason or who had not been admitted. The VEa for the prevention of hospitalisation for COVID-19 was 96.8% (95% CI [76.1%, 99.6%]). The other factors associated with the development of a severe SARS-CoV-2 infection are shown in Table 4.

4. Discussion

The results presented here provide two lines of evidence: on the one hand they indicate that after having completed a mRNA vaccine regimen against SARS-CoV-2 in a real-world situation outside of clinical trials,

Table 2
Factors associated with SARS-CoV-2 infection in health professionals ($n = 6364$).

	COVID-19 cases ($n = 1469$) n (%)	No COVID-19 cases ($n = 4895$) n (%)	Unadjusted OR 95% CI	p-value	Adjusted OR[a] 95% CI	p-value
Vaccinated						
Pfizer (full regimen) > 120 days	327 (22.3)	1516 (31.0)	0.30 (0.26–0.35)	< 0.001	0.28 (0.24–0.33)	< 0.001
Pfizer (full regimen) 12–120 days	107 (7.3)	1713 (35.0)	0.09 (0.07–0.11)	< 0.001	0.08 (0.07–0.10)	< 0.001
Moderna (full regimen) > 120 days	8 (0.5)	91 (1.9)	0.12 (0.06–0.25)	< 0.001	0.12 (0.06–0.24)	< 0.001
Moderna (full regimen) 12–120 days	5 (0.3)	144 (2.9)	0.05 (0.02–0.12)	< 0.001	0.05 (0.02–0.12)	< 0.001
Unvaccinated	1022 (69.6)	1431 (29.2)	1		1	
Sex (female)	1109 (75.5)	3751 (76.6)	0.94 (0.82–1.08)	0.369	1.16 (0.99–1.35)	0.060
Age						
≤ 39	566 (38.5)	2188 (44.7)	0.82 (0.68–0.99)	0.037	0.64 (0.52–0.79)	< 0.001
40–59	703 (47.9)	2071 (42.3)	1.08 (0.90–1.30)	0.406	0.97 (0.79–1.19)	0.972
≥ 60	200 (13.6)	636 (13.0)	1		1	
Professional category						
Medical practice	338 (23.0)	1260 (25.7)	0.91 (0.75–1.08)	0.265	1.26 (1.03–1.55)	0.025
Nursing	508 (34.6)	1570 (32.1)	1.09 (0.92–1.29)	0.332	1.43 (1.18–1.74)	< 0.001
Auxiliary staff/technicians	357 (24.3)	1171 (23.9)	1.03 (0.85–1.23)	0.792	1.14 (0.93–1.39)	0.214
Others[b]	266 (18.1)	894 (18.3)	1		1	
Professional setting						
Primary healthcare services	335 (22.8)	1080 (22.1)	1.04 (0.91–1.20)	0.549	1.13 (0.97–1.32)	0.125
Specialised care/others[c]	1134 (77.2)	3815 (77.9)	1		1	
Comorbidities						
Asthma	121 (8.2)	448 (9.2)	0.89 (0.72–1.10)	0.281	–	–
Cancer	47 (3.2)	221 (4.5)	0.69 (0.51–0.96)	0.028	0.69 (0.49–0.98)	0.039
Cerebrovascular disease	18 (1.2)	63 (1.3)	0.95 (0.56–1.61)	0.853	–	–
Diabetes	59 (4.0)	218 (4.5)	0.90 (0.67–1.20)	0.472	0.98 (0.71–1.36)	0.926
Chronic obstructive pulmonary disease	13 (0.9)	82 (1.7)	0.52 (0.29–0.94)	0.031	0.53 (0.28–1.00)	0.050
Liver disease	45 (3.1)	211 (4.3)	0.70 (0.51–0.97)	0.034	0.73 (0.51–1.04)	0.080
Immunosuppression	6 (0.4)	15 (0.3)	1.33 (0.52–3.45)	0.551	–	–
Obesity	120 (8.2)	429 (8.8)	0.93 (0.75–1.14)	0.476	–	–
Other respiratory diseases	6 (0.4)	26 (0.5)	0.77 (0.32–1.87)	0.561	–	–
Chronic renal disease	15 (1.0)	79 (1.6)	0.63 (0.36–1.10)	0.102	0.64 (0.35–1.17)	0.147
Tobacco use	121 (8.2)	490 (10.0)	0.81 (0.65–0.99)	0.043	0.78 (0.62–0.98)	0.034
Thalassemia	8 (0.5)	32 (0.7)	0.83 (0.38–1.81)	0.643	–	–
Transplant recipient	3 (0.2)	6 (0.1)	1.67 (0.42–6.68)	0.470	–	–

[a] OR adjusted for vaccination, sex, age, professional category, professional setting, cancer, diabetes, chronic obstructive pulmonary disease, liver disease, chronic kidney disease, and tobacco use.
[b] Guards, administrative staff, and maintenance staff.
[c] Municipal Emergency Assistance Service (SAMU), central services, general directorates, public health centres, and departmental management units.

Table 3
Adjusted vaccine effectiveness according to the time elapsed since the completion of the vaccination regimen ($n = 6364$).

	Pfizer complete 12–120 days	Pfizer complete > 120 days	Moderna complete 12–120 days	Moderna complete > 120 days
	VEa[a] (95% CI)	VEa[a] (95% CI)	VEa[a] (95% CI)	VEa[a] (95% CI)
Total	91.6% (89.6%–93.2%)	71.5% (67.0%–75.5%)	95.2% (88.3%–98.1%)	88.3% (75.7%–94.4%)
Sex				
Male ($n = 1504$)	95.2% (92.1%–97.0%)	76.3% (67.5%–82.7%)	97.1% (78.6%–99.6%)	94.7% (60.1%–99.3%)
Female ($n = 4860$)	90.2% (87.6%–92.3%)	70.5% (65.1%–75.1%)	94.5% (85.0%–98.0%)	85.8% (68.8%–93.5%)
Age				
≤ 39 ($n = 2754$)	92.5% (89.4%–94.8%)	73.7% (66.6%–79.3%)	91.7% (65.6%–98.0%)	68.4% (16.9%–88.0%)
40–59 ($n = 2774$)	90.3% (86.9%–92.8%)	73.1% (66.4%–78.4%)	96.5% (85.5%–99.1%)	92.6% (76.1%–97.7%)
≥ 60 ($n = 836$)	93.8% (88.6%–96.6%)	61.5% (42.6%–74.2%)	95.9% (69.3%–99.4%)	–
Professional category				
Medical practice ($n = 1598$)	93.1% (89.2%–95.5%)	73.4% (64.8%–79.9%)	–	88.5% (50.0%–97.3%)
Nursing ($n = 2078$)	92.1% (88.7%–94.5%)	75.4% (68.3%–81.0%)	94.2% (75.7%–98.6%)	76.2% (36.7%–91.1%)
Auxiliary staff/ technicians ($n = 1528$)	91.4% (86.4%–94.6%)	71.3% (60.3%–79.2%)	92.4% (68.3%–98.2%)	94.8% (61.5%–99.3%)
Others[b] ($n = 1160$)	89.2% (82.3%–93.4%)	59.7% (41.4%–72.3%)	95.4% (65.6%–99.4%)	–
Professional setting				
Primary care ($n = 1415$)	91.5% (86.7%–94.5%)	64.8% (53.1%–73.6%)	–	–
Specialised areas/ others[c] ($n = 4949$)	91.5% (89.2%–93.4%)	73.6% (68.5%–77.9%)	–	–
Comorbidities				
Asthma ($n = 569$)	94.9% (87.5%–97.9%)	73.3% (54.6%–84.3%)	–	–
Cancer ($n = 268$)	93.3% (79.4%–97.8%)	74.9% (40.9%–89.3%)	–	–
Cerebrovascular disease ($n = 77$)	–	–	–	–
Diabetes ($n = 277$)	87.6% (70.5%–94.8%)	79.3% (52.8%–90.9%)	–	–
Chronic obstructive pulmonary disease ($n = 95$)	98.3% (63.1%–99.9%)	97.3% (32.9%–99.9%)	–	–
Liver disease ($n = 256$)	94.1% (79.2%–98.3%)	67.9% (19.4%–87.2%)	–	–
Immunosuppression ($n = 20$)	–	–	–	–
Obesity ($n = 549$)	93.4% (85.6%–97.0%)	64.2% (39.3%–78.9%)	–	–
Other respiratory diseases ($n = 32$)	–	–	–	–
Chronic renal disease ($n = 94$)	96.2% (40.0%–99.8%)	30.1% (−312.2%–88.1%)	–	–
Tobacco use ($n = 611$)	91.0% (79.8%–96.0%)	56.0% (27.8%–73.2%)	–	–
Thalassemia ($n = 39$)	–	–	–	–
Transplant recipient ($n = 9$)	–	–	–	–

[a] Vaccine effectiveness adjusted for sex, age, professional category, asthma, cancer, diabetes, chronic obstructive pulmonary disease, liver disease, chronic kidney disease, and tobacco use.
[b] Guards, administrative staff, and maintenance staff.
[c] Municipal Emergency Assistance Service (SAMU), central services, general directorates, public health centres, and departmental management units.

the effectiveness of the vaccine to prevent SARS-CoV-2 infection decreases as time elapses from the moment of its administration. In the case of the Pfizer vaccine, the VE decreased from 91.6% when 12 to 120 days had elapsed since its administration, to 71.5% when >120 days had passed. For the Moderna vaccine, the comparable decrease from 95.2% to 88.3% was less obvious. Nonetheless, when considering the full regimen of both vaccines, their effectiveness to prevent hospitalisation for COVID-19 was 96.8%, and this VE was maintained over time.

Defining when a vaccine is effective is somewhat unspecific and is a complex task (Hodgson et al., 2021). The WHO suggested that 50% efficacy should be a minimum criterion for any COVID-19 vaccine, and that these criteria could be assessed with respect to disease severity or transmission (World Health Organization, 2022). There is previous evidence that the efficacy of the vaccine begins to become apparent early on. Indeed, based on data from the global BNT162b2 vaccine phase 2/3 trial, the cumulative incidence of COVID-19 cases over time began to diverge for the placebo versus BNT162b2 vaccine recipients as early as 12 days from the first dose, with the VE for preventing COVID-19 at this point being 52% (Polack et al., 2020). Moreover, efficacy data from 7 days after the second dose of the vaccine reached 94.8% (95% CI [89.8%, 97.6%).

Focussing on studies that globally assessed real world VE, an observational cohort study results in Italy that included >6136 HPs, concluded that the VE against infection was 94.8% (87.0–97.8%) after the second dose of BNT162b2 mRNA COVID-19 vaccine (Comirnaty) (Bianchi et al., 2021). Furthermore, a nationwide study of mRNA vaccines from the United States concluded that mRNA vaccines were highly effective in preventing cases of COVID-19, and yielded VE results of 82% to 94% (Pilishvili et al., 2021). Another study, performed in HPs from Israel, estimated that the VE 14 days after the second dose was 89% (95% CI, 83–93%) (Muhsen et al., 2021). Also in Israel, results of an observational study during nationwide vaccination campaign in residents aged 16 years or older, concluded that VE against hospitalisation for COVID-19 was estimated at 97,2% (95% CI: 96,8–97,5%) at 14 days or more after the second dose (Haas et al., 2021).

In terms of VE with respect to variations in the time elapsed from their administration, another retrospective cohort study conducted in HPs at the Mayo Clinic obtained VEa results exceeding 96% (Swift et al., 2021), which is also very consistent with our VE findings in the 12–120 group. A study in the general UK population (Andrews et al., 2022) reported a decrease in the VE of BNT162b2 for the prevention of SARS-CoV-2 infection as a function of the time elapsed after administration of the second dose; they reported figures ranging from 92.4% to 72.9% 10 weeks after completion of the regimen. Of note, as also observed in the data from this current study, these authors estimated that the VE for the prevention of hospitalisation was 93.5% and remained more stable

Table 4
Vaccine effectiveness and factors associated with hospitalisation for COVID-19 in health professionals ($n = 6364$).

	Hospital admission for COVID-19 ($n = 21$) *n* (%)	Admission for another reason/not admitted ($n = 6343$) *n* (%)	Unadjusted OR 95% CI	*p*-value	Adjusted OR[a] 95% CI	*p*-value	VEa[a] (95% CI)
Vaccinated							
Complete regimen	1 (4.8)	3910 (61.6)	0.03 (0.01–0.23)	< 0.001	0.03 (0.04–0.24)	< 0.001	96.8% (76.1%–99.6%)
Unvaccinated	20 (95.2)	2433 (38.4)	1		1		
Sex (female)	12 (57.1)	4848 (76.4)	0.41 (0.17–0.98)	0.044	2.68 (1.03–6.97)	0.043	
Age							
≤ 39	7 (33.3)	2747 (43.3)	0.26 (0.09–0.73)	0.010	0.35 (0.11–1.09)	0.071	
40–59	6 (28.6)	2768 (43.6)	0.22 (0.08–0.65)	0.006	0.25 (0.08–0.78)	0.017	
≥ 60	8 (38.1)	828 (13.1)	1		1		
Professional category							
Medical practice	1 (4.8)	1597 (25.2)	0.15 (0.02–1.24)	0.078	0.26 (0.03–2.34)	0.230	
Nursing	9 (42.9)	2069 (32.6)	1.00 (0.34–3.00)	0.993	1.92 (0.59–6.24)	0.277	
Auxiliary staff/technicians	6 (28.6)	1522 (24.0)	0.91 (0.28–2.99)	0.877	1.35 (0.38–4.82)	0.644	
Others[b]	5 (23.8)	1155 (18.2)	1		1		
Professional setting							
Primary healthcare services	5 (23.8)	1410 (22.2)	1.09 (0.40–2.99)	0.862	1.37 (0.46–4.08)	0.570	
Specialised area/others[c]	16 (76.2)	4933 (77.8)	1		1		
Comorbidities							
Asthma	2 (9.5)	567 (8.9)	1.07 (0.25–4.62)	0.925	–	–	
Cancer	2 (9.5)	266 (4.2)	2.41 (0.56–10.38)	0.240	–	–	
Cerebrovascular disease	4 (19.0)	77 (1.2)	19.15 (6.30–58.22)	< 0.001	12.67 (3.46–46.38)	< 0.001	
Diabetes	3 (14.3)	274 (4.3)	3.69 (1.08–12.61)	0.037	1.55 (0.38–6.35)	0.542	
Chronic obstructive pulmonary disease	0 (0.0)	95 (1.5)	Incalculable	–	–	–	
Liver disease	1 (4.8)	255 (4.0)	1.20 (0.16–8.93)	0.863	–	–	
Immunosuppression	0 (0.0)	21 (0.3)	Incalculable	–	–	–	
Obesity	6 (28.6)	543 (8.6)	4.27 (1.65–11.06)	0.003	4.77 (1.68–13.54)	0.003	
Other respiratory diseases	0 (0.0)	32 (0.5)	Incalculable	–	–	–	
Chronic renal disease	0 (0.0)	94 (1.5)	Incalculable	–	–	–	
Tobacco use	1 (4.8)	610 (9.6)	0.47 (0.06–3.51)	0.462	–	–	
Thalassemia	0 (0.0)	40 (0.6)	Incalculable	–	–	–	
Transplant recipient	0 (0.0)	9 (0.1)	Incalculable	–	–	–	

[a] OR adjusted for vaccination, sex, age, professional category, professional setting, cerebrovascular disease, diabetes, and obesity.
[b] Guards, administrative staff, and maintenance staff.
[c] Municipal Emergency Assistance Service (SAMU), central services, general directorates, public health centres, and departmental management units.

over time compared to the VE for the prevention of SARS-CoV-2 infection. Another study conducted in the context of Delta variant predominance that estimated VE according to the time since vaccination regimen completion (Fabiani et al., 2022) was also consistent with our study findings. These authors observed a decrease in the VE from 82% to 33% for the prevention of SARS-CoV-2 infection 27–30 weeks from the administration of the second dose, and a VE decrease from 96% to 80% for the prevention of hospitalisation for COVID-19. In the same sense, another study that assessed the VE in children and adolescents as well as its evolution over time (Klein et al., 2022) showed a VE reduction from 92% to 79%.

It is worth pointing out that this current study had several limitations. Firstly, our sample size was limited and therefore, the results cannot be generalised to larger populations. However, the fact that our results were consistent with other larger studies indicates that extrapolation of our data could be plausible. Second, we did not know the SARS-CoV-2 variant of each of the cases and so we could not assess the stratified VE in this sense because the variant sequencing was only done randomly in a given number of cases and therefore the variant of each of the HPs evaluated was not available. Notwithstanding, because of ongoing systematic variant genomic sequencing, we know that we completed this study when the Alpha and wild variants were dominant, prior to the dominance of the Delta variant in the Valencian Autonomous Community in epidemiological week 28. Third, given that the study population only included active HPs, there was no representation of the population aged over 65 years or of younger adolescents, children, or pregnant women. Notwithstanding, the strong points of this work were that we employed the negative test study design recommended by the WHO (World Health Organization, 2021), ECDC (European Centre for Disease Prevention and Control, 2021), and other organisations for the analysis of VE. Likewise, this design has also been successfully applied in the evaluation of other vaccination programs such as seasonal influenza (Foppa et al., 2013). Finally, we did not include the variable "history of SARS-CoV-2 infection" in the statistical analysis because the

design of the data extraction protocol only included the diagnosis of COVID-19 when there was infection that required hospital admission, so the data on previous infection in outpatients was not collected, and for this reason it was not possible to perform a stratified analysis which could overestimate VE.

Given the importance of vaccination as a disease prevention strategy, evaluating VE in the context of a real population rather than in a clinical trial is essential. This current work highlights the importance both of initial evaluations and of constant re-evaluation of VEs as time elapses. Work such as ours not only allows vaccination to be prioritised, but also helps researchers to define the next steps in prevention strategies, readjust implementation protocols, and suggest new guidelines to reinforce vaccination strategies, as required. It is vital that VE be evaluated on a global scale, both at the regional and state levels. Thus, promoting programs such as ProVaVac to evaluate VE allows such evaluations to be implemented in broader populations rather than being circumscribed to a single health department (Chico-Sánchez et al., 2022; Gras-Valentí et al., 2021).

5. Conclusions

Here we found that administration of the complete BNT162b2 or mRNA-1273 vaccine regimen against SARS-CoV-2 was highly effective for the prevention of COVID-19 cases in HPs when 12 to 120 days had elapsed since the second dose. Their effectiveness for the prevention of infection decreased as time passed from their administration, although VE was maintained for the prevention of serious infections. These results are consistent with, and reinforce the importance of, the vaccine prioritisation of different population groups established in the state vaccination strategy (Estrategia de vacunación frente a COVID-19 en España, 2022). These findings also establish the basis of organisational decisions involving the administration of booster regimens, especially for essential groups such as HPs. The continued evaluation of VE over extended periods of time is essential to verify if effectiveness continues to decrease and to evaluate what effect new predominant COVID-19 variants such as Delta or Omicron may have on VE.

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Authors' contributions

PC-S, PG-V, NA-S and JS-P conceived of the presented research idea. PC-S, PG-V and JS-P designed the statistical model, analysed the data and authored the first draft of the research manuscript. PC-S, PG-V, NA-S, NJ-S, HV, SP, JB, AB, DN and JS-P, carried out the data collection and provided project management support and reviewed the collected data for quality and reliability. HV, SP, JB, AB, DN contributed to the interpretation of the results. All authors provided critical feedback and helped shape the research, analysis and manuscript, including review and approval of the manuscript in its final form.

CRediT authorship contribution statement

Pablo Chico-Sánchez: Conceptualization, Investigation, Writing – review & editing, Methodology, Supervision, Project administration, Visualization, Writing – original draft. **Paula Gras-Valentí:** Conceptualization, Investigation, Writing – review & editing, Formal analysis, Project administration, Visualization, Writing – original draft. **Natividad Algado-Sellés:** Conceptualization, Investigation, Writing – review & editing, Data curation. **Natali Jiménez-Sepúlveda:** Conceptualization, Investigation, Writing – review & editing, Formal analysis. **Hermelinda Vanaclocha:** Conceptualization, Investigation, Writing – review & editing. **Salvador Peiró:** Conceptualization, Investigation, Writing – review & editing. **Javier S. Burgos:** Conceptualization, Investigation, Writing – review & editing. **Ana Berenguer:** Conceptualization, Investigation, Writing – review & editing. **David Navarro:** Conceptualization, Investigation, Writing – review & editing. **José Sánchez-Payá:** Conceptualization, Investigation, Writing – review & editing, Methodology, Supervision, Project administration, Visualization, Writing – original draft.

Declaration of Competing Interest

None.

Data availability

Data will be made available on request.

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