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Long term bivalent mRNA vaccine effectiveness against COVID-19 hospitalisations and deaths in Portugal: a cohort study based on electronic health records

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Abstract

Background In Autumn 2022, there were recommendations for a COVID-19 booster vaccination with adapted bivalent vaccines to eligible population. Evaluating vaccine effectiveness (VE), in a short period after the vaccination, is key to guide public health decisions on the vaccine performance, allowing implementation of mitigation strategies promptly. However, to assess long-term protection post-vaccination and evaluate the need for additional boosters, it is crucial to conduct studies that span the maximum duration of the vaccination program. This study aims to estimate the VE of bivalent mRNA vaccines against COVID-19-related hospitalisation and death in the Portuguese population aged 65 years or older, from September 2022 to May 2023.

Methods We used a cohort approach to analyse six electronic health registries using deterministic linkage, with a follow-up period of eight months. Severe outcomes included COVID-19-related hospitalisations and death, classified using discharge ICD-10 codes as proxies. The exposure of interest was the bivalent mRNA vaccine. VE was estimated for 14–97, 98–181 and 182–240 days after bivalent vaccination. Confounder-adjusted hazard ratio (aHR) was obtained by fitting a time-dependent Cox regression model with time-dependent vaccination status, adjusted for sociodemographic, history of influenza and pneumococcus vaccination, previous SARS-CoV-2 tests and infection, and comorbidities. VE was estimated by one minus the aHR between vaccinated with bivalent vaccine person-years versus those without bivalent vaccine person-years.

Results The cohort included 2,151,531 individuals aged 65 or older (27.8% with 80 or more years). In the ≥ 80 years old, VE was 41.3% (95%CI: 34.5–47.5%) and 50.3% (95%CI: 44.6–55.3%) against COVID-19-related hospitalisation and

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death, respectively. In the 65–79 years old, VE was 58.5% (95%CI: 51.9–64.2%) against COVID-19-related hospitalisation, and 65.1% (95%CI: 59.0–70.4%) against COVID-19-related death. VE waned for both age groups and outcomes. Among adults aged 65 years or older, we observed long-term moderate VE estimates against severe COVID-19-related outcomes.

Conclusions These results support the need for yearly boosters of COVID-19 vaccination to maximise the protection of the senior population against COVID-19 severe disease. Additional (spring boosters) during a vaccination campaign should be evaluated considering the epidemiological context and results from long-term VE studies.

Keywords COVID-19, Vaccine effectiveness, Electronic health records, Cohort, Portugal

Introduction

On September 6 2022, Portuguese health authorities recommended COVID-19 booster vaccination with adapted bivalent mRNA vaccines to those aged 60 or more [1] to match the circulating virus variant and thus prevent severe complications after Omicron SARS-CoV-2-related infection. The first available bivalent vaccine was from Comirnaty Original/BA.1 [2], followed by Comirnaty Original/ BA.4–5 [3] and Spikevax Original/BA.1 [4]. The last approved vaccine was Spikevax Original/BA.4–5 (late November 2022). Only individuals who have completed at least a primary vaccination were eligible for the seasonal booster, regardless of their previous history of booster uptake. Another criteria, was a minimum period of three months after a previous SARS-CoV-2-related event (infection or vaccination) before being eligible for the seasonal booster. The vaccination campaign was rolled out by age criteria, prioritising those aged 80 and over. Considering primary series vaccination campaign, it started in February 2021 and achieved extremely high vaccine coverage, with more than 90% of the 65 and older being considered completely vaccinated [5]. Throughout the pandemic, different booster doses were recommended to this group of the population, but the spring booster in May 2022, was only recommended to the 80 and more years old [6] (reaching a 68% coverage by isoweek 36 2022) [5].

In September 2022, the epidemiological situation in Portugal was characterised by the predominant circulation of the Omicron BA.5 variant. During the autumn and winter months, the BA.5 variant decreased in frequency, and the XXQ variant surged in week 40/2022. By week 10/2023, more than 50% of the sequenced virus were classified as Omicron- XBB variant [7]. XBB variant has been described as a potential increase in immunity evasion [8].

In the context of introducing new vaccines, different variants in circulation, and preparing future vaccination campaigns, evaluating the protection against severe COVID-19 outcomes granted by the vaccine used in the national programme, particularly in the population aged 65 and more years is crucial. Early vaccine effectiveness (VE) estimates, in a short period after the vaccination

campaign implementation, indicated moderate to high VE against severe outcomes [9–11]. These estimates are extremely informative for decision-makers on the short term performance of a given vaccine and allow the implementation of other mitigation strategies promptly in case of low protection. However, and given the pattern of decreasing VE from 1 month to 6 months after full vaccination [12], this early evaluation tends to measure the vaccine performance during a period of maximum VE. To gain a broader perspective of VE and assess long-term protection post-vaccination, it is crucial to conduct studies that span the entire duration of the vaccination program. Thus, we aimed to estimate the VE of the adapted bivalent mRNA vaccines against COVID-19-related hospitalisation and death for the Portuguese population aged 65 and over and by time since vaccination between September 7, 2022 and May 31, 2023.

Materials and methods

Study design

Using electronic health registries, we used a cohort approach to estimate the VE of bivalent mRNA booster. The study design was described in detail in previous studies [13–15]. To summarise, a individual-level deterministic data linkage of six nationwide electronic health registries (the National Health Service User (NHSU) database, the national vaccination registry (VACINAS), the National Information System for Epidemiologic Surveillance (SINAVE), the National Death Registry (SICO), the Primary Information System (SIM@SNS), and the national database of hospital discharges (BIMIH)) was done using the unique national health number identifier for National Health System (NHS). (Supplementary material, Table S1)

The target population included residents in mainland Portugal aged 65–110 years who completed at least the primary vaccination scheme and were eligible for bivalent booster vaccination. We excluded non-users of the in the past three years, individuals infected with SARS-CoV-2 within 90 days before the start of the follow-up, individuals vaccinated with monovalent vaccines within 90 days before the start of the vaccination campaign, individuals vaccinated with the monovalent vaccines during the

follow-up period, and with incomplete or inconsistent information on vaccination (i.e., the interval between the two doses for primary vaccination was less than 19 days, brands were not recommended in Portugal, the interval

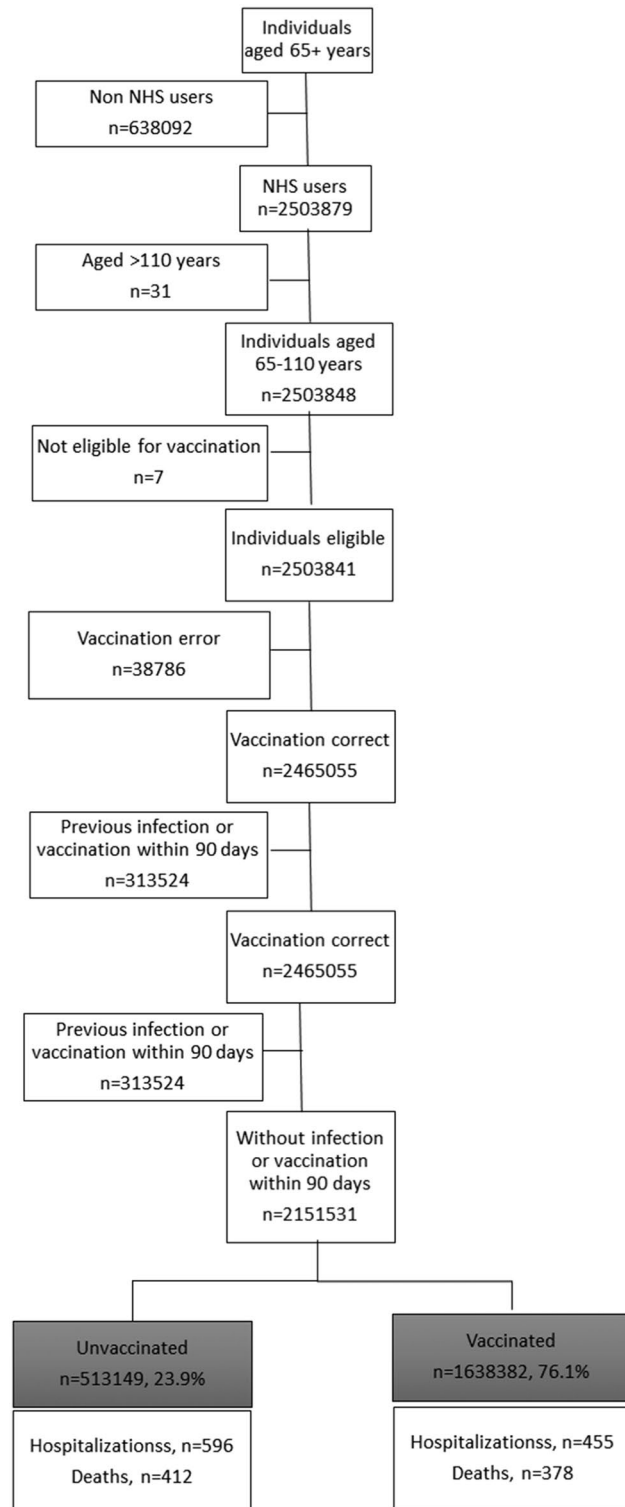


Fig. 1 Flowchart of the selection process to design the cohort for analysis

between successive booster vaccinations was less than 90 days, the combination of brands were not recommended, vaccinated with bivalent vaccines before authorisation in Portugal, and partially vaccinated— only with one dose instead of two doses, for two doses vaccine) (Fig. 1).

Based on the vaccination campaign calendar, the follow-up period was between September 7, 2022 and May 31, 2023. The data extraction and linkage for this study were performed by the Shared Services of the Ministry of Health (SPMS) on July 27, 2023 to allow data consolidation.

Outcome and exposure

The outcomes of interest included COVID-19 hospitalisation, defined as an admission to a hospital for at least 24 h following laboratory-confirmed infection with SARS-CoV-2 and having COVID-19 as the primary diagnosis at discharge (ICD10 coding U071), and COVID-19-related death, defined as death for which COVID-19 was recorded as the cause of death (U071) or deaths that occurred within 30 days after the laboratory-confirmed SARS-CoV-2 infection.

The exposure was an uptake of bivalent mRNA vaccine (Comirnaty Origin/BA.1, Comirnaty Origin/BA.5, Spikevax Origin/BA.1, Spikevax Origin/BA.5). Individuals were considered vaccinated 14 days following a bivalent mRNA vaccine uptake. Time since the bivalent vaccine was considered to evaluate the hypothesis of VE waning, VE was estimated for 14–97 days, 98–181 days and 182–240 days after bivalent vaccination.

Statistical analysis

Individuals and person-years of individuals eligible for the bivalent booster but without it were considered the reference group, hereafter referred to as “without bivalent vaccine”.

At the end of the follow-up period, participants were characterised according to their exposure using absolute and relative frequencies. VE was estimated by one minus the confounder-adjusted hazard ratio (aHR) between vaccinated with bivalent vaccine person-years versus without bivalent vaccine person-years ($VE = 100 * (1 - aHR)$). Confounder-adjusted hazard ratios were obtained by fitting a time-dependent Cox regression model, with time-dependent vaccine status and further adjusted for sex, age group, region, municipality deprivation index quintile, history of influenza and pneumococcus vaccination in the previous three years, number of COVID-19 tests in 2020–2022, comorbidities (i) none, ii) low/medium risk—at least one of the following conditions without immunosuppression, i.e., anaemia, dementia, diabetes, cardiac disease, neuromuscular disease, rheumatologic disease, obesity, tuberculosis, stroke, pulmonary disease, asthma, liver disease and hypertension, and high risk—at least one

of the following immunocompromising conditions, i.e., HIV, renal disease, and cancer), previous SARS-CoV-2 infection (previous positive test before the start of the follow up). Calendar time was included as strata in the

Table 1 Description of the population during the study period—September 7, 2022 to March 31, 2023

	Without bivalent vaccine No. 513,149	With bivalent vaccine No. 1,638,382
Age (years), median (IQR)	73.0 (68.0–79.0)	74.0 (69.0–81.0)
Age group, (%)		
65–69	169,026 (32.9%)	411,519 (25.1%)
70–74	124,841 (24.3%)	414,041 (25.3%)
75–79	94,596 (18.4%)	338,853 (20.7%)
80–84	62,358 (12.2%)	230,856 (14.1%)
85–89	41,460 (8.1%)	156,310 (9.5%)
90–94	16,643 (3.2%)	68,077 (4.2%)
95+	4,225 (0.8%)	18,726 (1.1%)
Sex Male, n (%)	198,108 (38.6%)	732,171 (44.7%)
Region, n (%)		
A.R.S. Alentejo	31,100 (6.1%)	84,887 (5.2%)
A.R.S. Algarve	38,977 (7.6%)	60,447 (3.7%)
A.R.S. Centro	99,911 (19.5%)	313,052 (19.1%)
A.R.S. LVT	175,873 (34.3%)	571,935 (34.9%)
A.R.S. Norte	161,128 (31.4%)	600,853 (36.7%)
Missing	6,160 (1.2%)	7,208 (0.4%)
EDI Quintile, n (%)		
Q1 (least deprived)	74,745 (14.6%)	255,425 (15.6%)
Q2	77,970 (15.2%)	245,686 (15.0%)
Q3	76,846 (15.0%)	241,289 (14.7%)
Q4	134,906 (26.3%)	474,169 (28.9%)
Q5 (most deprived)	142,522 (27.8%)	414,605 (25.3%)
Missing	6,160 (1.2%)	7,208 (0.4%)
Comorbidity, n (%)		
None	126,964 (24.7%)	304,773 (18.6%)
Low/médium risk	279,885 (54.5%)	908,963 (55.5%)
High risk	106,300 (20.7%)	424,646 (25.9%)
Number of SARS-CoV-2 tests, n (%)		
0	200,685 (39.1%)	518,258 (31.6%)
1	109,869 (21.4%)	346,270 (21.1%)
2	68,827 (13.4%)	237,301 (14.5%)
3	42,279 (8.2%)	156,393 (9.5%)
4–9	73,734 (14.4%)	300,454 (18.3%)
10+	17,755 (3.5%)	79,706 (4.9%)
Any other vaccine, n (%)†	288,735 (56.3%)	1,493,959 (91.2%)
Previous infection, n (%)	95,070 (18.5%)	436,656 (26.6%)
Vaccine type, n (%)		
Spikevax Origin/BA.1	NA	70,440 (4.3%)
Comirnaty Origin/BA.1	NA	867,415 (52.9%)
Comirnaty Origin/BA 4–5	NA	700,527 (42.8%)

A.R.S.— Regional Health Administration (Administração Regional de Saúde). †received at least one of the following vaccines since 2019: influenza, PN23, PCV7, 10 or 13. NA— not applicable

model, considering intervals of 14 days. Individuals who died of any cause before the end of the study were censored. When the outcome was COVID-19-related death, only individuals who died of other causes were censored. Complete case analysis was used.

Data analysis was performed with R software, version 4.0.5 (R Foundation, Vienna, Austria). The statistical significance level was set at 5%.

Ethical statement

The study received approval from the Ethical Committee and the Data Protection Officer of the National Institute of Health Doutor Ricardo Jorge (December 13, 2022), the need for the participants' informed consent was waived by the Ethical Committee. All data were anonymised by the SPMS before being made available for statistical analysis. Due to the sensitive nature of the personal health information used by this study, individual-level data that support the findings of this study is not publicly available.

Results

We included in the analysis 2,151,531 individuals aged 65–119 years, 513,149 unvaccinated, and 1,638,382 vaccinated with the bivalent booster by May 2023. The vaccine rollout (Supplementary material, Figure S1) indicates that the maximum vaccine uptake plateau was achieved in mid-November for the 80 and more years (2 month after vaccination started) and mid-December for the 65–79 years (3 months after vaccination started). Considering vaccinated individuals, 52.9% had received the Comirnaty Origin/BA.1, 42.8% the Comirnaty Origin/BA 4–5 and 4.3% the Spikevax Origin/BA.1. Their distribution over time were in accordance with the availability and respective disposal of each vaccine brand/composition (Supplementary material, Figure S2).

The comparison of individuals with and without bivalent vaccines revealed a higher proportion of comorbidities and older age among unvaccinated (Table 1).

A total of 2,865 COVID-19 hospitalisations (36.7% in the 65–79 years) and 2,615 deaths (30.2% in the 65–79 years) were registered during the follow-up period. The distribution of COVID-19 hospitalisations and COVID-19-related deaths can be seen in the Supplementary Material (Figures S3 and S4, respectively).

For the period in analysis, bivalent VE was estimated as 41.3% (95%CI: 34.5–47.5%) and 58.5% (95%CI: 51.9–64.2%) in the 80 and more years and 65–79 years, respectively. Considering COVID-19-related death, bivalent VE was 50.3% (95%CI: 44.6–55.3%) and 65.1% (95%CI: 59–70.4%) in the 80 and more years and 65–79 years, respectively (Table 2).

We observed a decline in VE over time for both outcomes and age groups (Table 3). Considering COVID-19 hospitalisation, 14–97 days after bivalent vaccine uptake,

Table 2 Bivalent vaccine effectiveness against COVID-19-related hospitalisation and death in the population aged 65 to 110 years, Portugal, September 2022 to May 2023

	Person-years	Events	VE (%)	VE 95%CI
COVID-19 hospitalisation				
65–79 years				
Without bivalent vaccine	426,633.6	596	Reference	
With bivalent vaccine	649,255.6	455	58.5	(51.9 to 64.2)
≥ 80 years				
Without bivalent vaccine	120,764.9	644	Reference	
With bivalent vaccine	282,939.9	1,170	41.3	(34.5 to 47.5)
COVID-19-related deaths				
65–79 years				
Without bivalent vaccine	426,836.7	412	Reference	
With bivalent vaccine	649,399.8	378	65.1	(59 to 70.4)
≥ 80 years				
Without bivalent vaccine	120,944.2	633	Reference	
With bivalent vaccine	283,204.5	1,192	50.3	(44.6 to 55.3)

VE– vaccine effectiveness, CI– confidence interval

VE reached the maximum of 66.5% (95%CI: 59.8–72.2%) and 46.9% (95%CI: 39.3–53.6%) for 65–79 and 80 or more years old, respectively. VE declined 182 or more days after vaccination to 33.8% (95%CI: 7.1–52.9%) and 29.8% (95%CI: 11.3–44.4%), respectively. Finally, VE against COVID-19-related death peaked at 75.1% (95% CI: 68.8–80%) for 65–79 years old and decreased to 52.7% (95%CI: 33.4–66.5%) 182 days after vaccine uptake. The corresponding figures for 80 and more years old were 55.7% (95%CI: 49.2–61.3%) 14–79 days after vaccination, and 39.3% (95%CI: 25.1–50.8%) 182 and more days after vaccination.

Discussion

This study provided a comprehensive overview of the effectiveness of the bivalent COVID-19 vaccine against severe COVID-19 in the Portuguese population aged 65 to 110 years over an 8-month follow-up period during autumn 2022 and winter/spring 2023. Overall, our results indicated moderate (VE point estimates ranged from approximately 41–65%, depending on the age group) against severe outcomes such as COVID-19-related hospitalisation or death. Our results support evidence of protection of the bivalent vaccine against hospitalisation or death.

Our estimates are lower compared to the early reports, September 2022 to January 2023, in individuals aged 65 or more years from Israel (VE of 72% and 68% against

Table 3 Bivalent vaccine effectiveness against hospitalisation and death, by time since bivalent vaccine uptake, in the population aged 65 to 110 years, Portugal, September 2022 to May 2023

	Person-years	Events	VE	VE 95%CI
COVID-19 hospitalisation				
65–79 years				
without bivalent vaccine	426633.6	596	Reference	
Time since bivalent vaccination				
14 to 97 days	265792.9	202	66.5	(59.8 to 72.2)
98 to 181 days	260169.5	173	46.5	(32.7 to 57.5)
182 to 240 days	123293.2	80	33.8	(7.1 to 52.9)
≥ 80 years				
without bivalent vaccine	120764.9	644	Reference	
Time since bivalent vaccination				
14 to 97 days	107332.6	518	46.9	(39.3 to 53.6)
98 to 181 days	103574.4	440	34.6	(23.3 to 44.2)
182 to 240 days	72032.9	212	29.8	(11.3 to 44.4)
COVID-19-related deaths				
65–79 years				
without bivalent vaccine	426836.7	412	Reference	
Time since bivalent vaccination				
14 to 97 days	265830.9	130	75.1	(68.8 to 80)
98 to 181 days	260231.5	169	49.4	(35.4 to 60.3)
182 to 240 days	123337.4	79	52.7	(33.4 to 66.5)
≥ 80 years				
without bivalent vaccine	120944.2	633	Reference	
Time since bivalent vaccination				
14 to 97 days	107380.8	479	55.7	(49.2 to 61.3)
98 to 181 days	103686.3	434	45.7	(36.4 to 53.6)
182 to 240 days	72137.4	279	39.3	(25.1 to 50.8)

VE– vaccine effectiveness, CI– confidence interval

hospitalisation and death, respectively) [9] and 10-month follow-up study in four European Nordic countries (VE ranging from 65.8 to 70% against severe outcomes) [16]. They are also lower compared to meta-analysis study effectiveness on bivalent mRNA booster vaccines against Omicron variants (72.0%; 95% CI: 51.4–83.9%) [17].

The low to moderate overall VE estimates observed within our study may be due to several factors. Although it is difficult to disentangle waning protection over time since vaccination and differential protection by variants, as these aspects are highly correlated in calendar time, these two factors may explain our results. For instance, regarding the effect of variants in circulation, Fabiani et al. [18] reported a VE of 45.6% against severe outcomes in the 60 and more years population during a period of predominant circulation of XBB variant, and a significant decay of VE estimates to 14.3% after 181 to 265 days of vaccination. We followed a cohort of the older adult population for an extended period (more than eight months), covering the circulation of different Omicron variants (namely the XBB variants), which may partially explain the different results obtained.

For both age groups, our results show consistent and significant VE wane for all observed COVID-19 outcomes. After approximately 3 to 6 months of vaccine uptake, we observed a significant decay in VE to low to moderate levels of protection against COVID-19 hospitalisation and death. This VE waning pattern was described for primary vaccination and booster doses, with levels of protection gradually declining over time [12] and has also been reported for the bivalent vaccine with VE against Omicron variants estimates of 38.4% after 5 months of vaccine uptake [19] and VE against hospitalisation of 35.9% after 2.5 months of the immunisation [11]. This consistent pattern has implications in designing and implementing COVID-19 vaccination campaigns if countries adopt an influenza-like yearly immunisation. Considering the 2022/2023 COVID-19 vaccination campaign, most European countries started vaccinating high-risk individuals in September (combining both influenza and COVID-19 vaccines). According to the VE wane pattern, this would imply that vaccine protection would be lower by December, which could be prejudicial if the administered vaccine has moderate effectiveness (in the period of maximum vaccine protection).

Concerning age, and contrary to what was reported by Fabiani et al. [18], we observed higher VE estimates for individuals aged 65–79 than for those 80 and more years for all outcomes included in this study. Several factors could contribute to observed differences in levels of conferred protection, such as immunosenescence and consequent deterioration in immune system function due to age [20]. However, it should be noted that the vaccination campaign rollout in Portugal also resulted in different vaccination histories for these age groups. In response to BA.5 Omicron emergence, national authorities recommended a monovalent 2nd booster for the 80 and more year population in mid-May 2022, while this recommendation did not target those 65–79 years old. By mid-May, when seasonal vaccination with bivalent vaccines started, the 2nd monovalent booster coverage in the 80 and more years group reached 68%. Hence, the reference group in 80 and more years included individuals more recently vaccinated than 65–79 (targeted by a 1st booster in November–December 2021). Thus, the lower VE estimates observed in the ≥ 80 -year-olds should also be interpreted in light of the reference group used for the estimation, i.e., individuals with high vaccine coverage (both primary series and multiple boosters). Additionally, vaccines administered at the beginning of the bivalent vaccine campaign included the BA.1 component, as 80 and more years were prioritised for vaccination. This age group might have a higher proportion of the BA.1 vaccine, which was mismatched with the circulating SARS-CoV-2 variant in the early season. Although similar VE

were reported by [16] for both vaccine compositions, the vaccine composition may still have some role in the overall VE measured in the population.

Our study has some limitations that should be acknowledged. First, it is based on routine healthcare databases, so data was not collected for research purposes. This fact could introduce misclassification bias in the measure of vaccine status, the outcomes and confounding variables. To increase the internal validity of the measured variables, we restricted our analysis to the NHS users, i.e., individuals with at least one contact with the NHS in the last three years. This procedure was done assuming that the quality of the measured variables in health electronic records would be high among those with regular contact with the health care system. On the other hand, excluding individuals with no contact with the NHS in the last three years could eventually introduce a selection bias. By comparing the total number of individuals in our cohort ($n=2,151,531$) with the total population aged 65 or older, according to official Statistics Portugal, ($n=2,414,904$) and adjusting for the primary series vaccine coverage in this age group (99.1%) results in 2,393,170 vaccinated individuals. We can see that our cohort covers 90% of the total target population. Supplement material, Table S2 compares the distribution of the population and our cohort, by age group and sex. Considering the similarities, we do not consider that the restriction on NHS users has introduced severe bias in our VE estimates. Besides this restriction, we should also mention the possibility of outcome misclassification bias related to hospitalisations coding at discharge. If the vaccine status is associated with a lower length of hospitalisation, the hospitalisations could be updated more frequently in the bivalent vaccinated group, which would bias the VE toward a null effect. Additionally, given the time needed for ICD-10 coding, the number of hospitalisation events could be underestimated. To overcome this, we used data extracted in July 2023 to measure VE until May 2023.

The role of previous infection in COVID-19 VE studies has been mentioned as introducing confounding bias or modifying the effect of the current vaccination. In this study, we excluded from the analysis the individuals with a previously recorded infection in the 90 days before the study started, given that they were not eligible to receive the bivalent COVID-19 vaccine. However, asymptomatic infections and self-tests done at home might not be reported on the health electronic records, underestimating the frequency of individuals with previous infections. This fact would challenge our ability to measure the vaccine effect modification by previous infection, given that we cannot roll out the presence of individuals with previous infection in the group without a documented previous infection. Considering that previous infection has an effect on the risk of COVID-19 hospitalisations [21],

knowledge by the individual or the health system of the previous infection status could change their probability of vaccine uptake. Considering this, known previous infections can introduce confounding bias, so we adjust for previous infections that occurred more than 90 days ago. Nevertheless, given the use of self-tests in the population, we cannot roll out the presence of misclassification of the variable known previous infection, which could introduce residual confounding bias. We expect that some individuals without bivalent vaccines can have a known previous infection that has not been recorded in EHR. This fact would reduce VE, as natural immunity would still protect them. Additionally, Portugal changed the testing strategy during the study period, focusing on respiratory infection diagnosis and then on screening groups of the population [22], which might have affected our outcomes, resulting in fewer deaths attributed to COVID-19 and, as a consequence, reducing outcome sensitivity, which would mainly affect the power of our estimates. Although we adjusted for several other confounding variables, residual confounding might be present due to unmeasured confounders.

Conclusions

Our results show that in Portugal, during the eight months after the COVID-19 vaccination campaign started, bivalent VE achieved moderate to high (47–75%) levels of protection against severe COVID-19 outcomes in the population aged 65 years or more. Six to eight months after, a decay in VE against severe disease was observed (30–53%). These results support the need for yearly boosters of COVID-19 vaccination to maximise the protection of the senior population against COVID-19 severe disease. Additional (spring boosters) during a vaccination campaign should be evaluated considering the epidemiological context and results from long-term VE studies.

Abbreviations

aHR	Confounder-adjusted hazard ratio
NHS	National Health System
VE	Vaccine effectiveness

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12879-025-10866-x>.

Supplementary Material 1

Acknowledgements

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Author contributions

AM IK drafted the manuscript and contributed equally to this article. IK AM BN conceptualized the study. SM was responsible for the data linkage and data extraction. PS BN IK performed a statistical analysis of the data. AM, BN, IK, SM, PS and members of PT-EHR vaccine group contributed to the results interpretation critically revised and approved the current version of the manuscript.

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Data availability

The data that support the findings of this study are available from SPMS (Serviços Partilhados do Ministério da Saúde, E.P.E.) but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of SPMS.

Declarations

Ethics approval and consent to participate

The study received approval from the Ethical Committee and the Data Protection Officer of the National Institute of Health Doutor Ricardo Jorge (December 13, 2022), the need for the participants' informed consent was waived by the Ethical Committee.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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