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COVID-19 vaccines effectiveness against symptomatic disease and severe outcomes, 2021–2022: a test-negative case–control study

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ABSTRACT

Objectives: This study evaluated the effectiveness of COVID-19 vaccines in preventing symptomatic and severe disease.
Study design: This was an observational test-negative case–control study.
Methods: Study participants were adults with at least one symptom included in the World Health Organization COVID-19 definition who sought health care in a public emergency department between 1 November 2021 and 2 March 2022 (corresponding with the fifth pandemic wave in Portugal dominated by the Omicron variant). This study used multivariable logistic regression models to estimate and compare the odds ratio of vaccination between test-positive cases and test-negative controls to calculate the absolute and relative vaccine effectiveness.
Results: The study included 1059 individuals (522 cases and 537 controls) with a median age of 56 years and 58% were women. Compared with the effectiveness of the primary vaccination scheme that had been completed ≥180 days earlier, the relative effectiveness against symptomatic infection of a booster administered between 14 and 132 days earlier was 71% (95% confidence interval [CI]: 57%, 81%; $P < 0.001$). The effectiveness of the primary series against symptomatic infection peaked at 85% (95% CI: 56%, 95%) between 14 and 90 days after the last inoculation and decreased to 34% (95% CI: −43%, 50%) after ≥180 days.
Conclusions: Despite the known immunological evasion characteristics of the Omicron variant, results from this study show that vaccine effectiveness increases after booster administration. COVID-19 vaccine effectiveness decreases to less than 50% between 3 and 6 months after completion of the primary cycle; therefore, this would be an appropriate time to administer a booster to restore immunity.

Introduction

Real-world studies have revealed that COVID-19 vaccines offer excellent short-term protection against human SARS-CoV-2 infection and its severe consequences, including hospitalisation and death.[1,2] In addition, vaccination and non-pharmacological measures have resulted in fewer people requiring hospitalisation, despite the latest high-incidence waves.[3] However, recently, concerns have been raised regarding the reduced effectiveness of the vaccines against new variants of concern.[4] Moreover, there is evidence that protection against symptomatic disease wanes over time.[5,6]

Results regarding booster protection against severe COVID-19 due to the Omicron variant are inconsistent. Some studies have

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suggested robust protection similar to the effectiveness against prior variants,[7,8] while other studies have reported reduced protection against the Omicron variant and further reduction over time after the booster dose.[9–11]

The vaccination campaign in Portugal started on 27 December 2020 with the Comirnaty vaccine developed by Pfizer-BioNTech, Mainz, Germany/New York, USA, followed by Spikevax from Moderna, Cambridge, USA, in the first weeks of January 2021, Vaxzevria from AstraZeneca, Cambridge, UK, on 7 February 2021 and Jcovden from Janssen, Beerse, Belgium, on 14 April 2021. Thus, these were the four vaccines approved for use in the EU/EEA during the data collection period.

This test-negative case–control study aims to evaluate the effectiveness of COVID-19 vaccines in preventing symptomatic and severe disease in Alto Minho, Portugal, during the fifth pandemic wave.[12]

Methods

Participants

Study participants were individuals aged ≥18 years who were residents of Alto Minho, had at least one symptom included in the World Health Organization (WHO) COVID-19 definition,[13] sought health care in a public emergency department in the region between 1 November 2021 and 2 March 2022, and were tested for SARS-CoV-2 using respiratory samples. Alto Minho is a Nomenclature of Territorial Units (NUTS) III region with 231,293 inhabitants according to the 2021 census[12] and is located in the Northern region of Portugal. This region was one of the most affected regions in Portugal and where the first cases of COVID-19 arose. A local approach was used for this study to enable access to more detailed and complete data.

Exclusion criteria included individuals who were not eligible for vaccination against COVID-19, those with unavailable laboratory test results, those without information on vaccination status and those with a symptom onset of more than 10 days before the test date. In addition, all individuals who had previously tested positive for COVID-19 were excluded from the analysis to minimise bias caused by natural immunity.

Study design

In this test-negative case–control study, the effectiveness of COVID-19 vaccines against symptomatic and severe SARS-CoV-2 infection was estimated, as described in detail elsewhere.[14] In brief, study participants were divided into two groups: SARS-CoV-2 test-positive cases and test-negative controls. Vaccination status between participants with symptomatic COVID-19 and those with reported symptoms but with a negative test result were compared. In addition, vaccination status between the patients with moderate-to-severe COVID-19 and those with mild COVID-19 were also compared.

Outcomes

The following were considered as the primary outcomes:

(1) Symptomatic SARS-CoV-2 infection confirmed with rRT-PCR tests, antigen tests or Xpress RT-PCR tests performed on respiratory samples from the nasopharynx or oropharynx; and
(2) Moderate-to-severe disease associated with SARS-CoV-2 infection defined by hospitalisation over 24 h, intermediate or intensive care unit (I/ICU) admission or death with a recent positive test result.

Hypothesis

The hypothesis questions tested were as follows:

(1) Is the effectiveness of COVID-19 vaccines against symptomatic disease due to the Omicron variant higher than 50%?; and
(2) Does the effectiveness of COVID-19 vaccines wane over time?

Sample size

According to the WHO guidelines,[15] the minimum sample size (N_1) in a test-negative case–control study should be calculated using the following formula:

$$N_1 = (z/d)^2[1/A(1-A)+1/CP_2(1-P_2)]$$

where C is the control-to-case ratio; P_2 is the prevalence of vaccine exposure in the control group (i.e. vaccine coverage in the population being studied); $A = P_2(1-VE)/[1-P_2(VE)]$, where VE denotes the anticipated effectiveness of the vaccine; z denotes the (1-α) percentage point of the standardised normal distribution (normally, this is based on an α-value of 0.05 and thus a z-value of 1.96); and d is determined by solving the equation $W(\hat{\beta},\hat{d}) = \exp(\hat{\beta})(\exp(\hat{d}) - (\exp(-\hat{d}))$ where $\hat{d} = z\hat{\sigma}$ and where and $W(\hat{\beta},\hat{d})$ denotes the confidence interval width. The number of controls needed is then calculated as $C*N_1$.[15]

Therefore, assuming a vaccine coverage of 90%, as the vaccine coverage for primary series vaccination was 88% in mainland Portugal in the middle of the study period, this study needed a sample size of at least 580 cases and 580 controls to detect an anticipated vaccine effectiveness (VE) of 70%, with a precision estimate of ±10%, and a type 1 error probability of 0.05.

Data sources

Databases extracted from Clinidata were used to identify all SARS-CoV-2 tests performed in the public emergency departments in Alto Minho during the study period. Participants' vaccination status were obtained from the national vaccination registry, including the type of vaccine, number of doses and date of inoculation. These and other clinical and sociodemographic variables were complemented with data from patients' electronic medical records and from the national platform of contact tracing (Trace COVID-19).

Covariates

Health and demographic data were collected, including age, sex, municipality of residence and comorbidities that confer an extremely vulnerable status,[16] including the following: (1) solid organ transplant receptors under long-term immunosuppression; (2) patients with active cancer under chemotherapy/radiotherapy or radical radiotherapy for lung cancer; (3) individuals under immunotherapy or other continuous antibody treatments for cancer; (4) patients under other directed cancer treatments that affect the immunological system, such as kinase protein or poly (ADP-ribose) polymerase inhibitors; (5) patients with haematologic cancer with leukaemia, lymphoma or myeloma in any treatment stage; (6) patients who have undergone bone marrow transplant or

stem cell treatment in the last 6 months or who are currently under immunosuppressive treatment; (7) patients with severe respiratory disease, including severe asthma and severe chronic obstructive pulmonary disease; (8) individuals with cystic fibrosis or idiopathic pulmonary fibrosis, regardless of disease stage; (9) patients with a rare disease and innate errors in metabolism that substantially increase the risk of infection (e.g. severe combined immunodeficiency and homozygotic sickle cell disease); (10) patients prescribed immunosuppressive therapy in the last 6 months; and (11) pregnant women with significant congenital heart disease.

The study sample included individuals who were (a) either unvaccinated or vaccinated with one dose less than 14 days before the symptom onset; (b) vaccinated with one dose of mRNA vaccine or Vaxzevria at least 14 days before the symptom onset or vaccinated with two doses of mRNA vaccine or Vaxzevria less than 14 days before the symptom onset (partially vaccinated); (c) vaccinated with two doses or one dose of Jcovden at least 14 days before the symptom onset (fully vaccinated) or vaccinated with a booster less than 14 days before the symptom onset; or (d) vaccinated with three doses or with Jcovden and a booster at least 14 days before the symptom onset.

Statistical analyses

In the univariate analysis, the Mann–Whitney test was used for continuous variables (age and time) and the chi-squared test or Fisher's exact test (every time there was a cell with under 10 observations) for categorical variables.

Multivariable logistic regression models were used to estimate and compare the odds ratios (ORs) of vaccination between the test-positive cases and test-negative controls; unvaccinated individuals were considered as a reference group for calculation of the absolute effectiveness and primary scheme completion between 14 and 179 days or ≥180 days earlier as a reference group for calculation of the relative effectiveness of a booster dose. The crude and adjusted ORs were estimated, accounting for all covariates, which were selected based on their known association with SARS-CoV-2 infection or severity and receipt of a COVID-19 vaccine,[16,17] and were assessed as potential confounders. VE was calculated using the following formula:

$$VE = (1-aOR) \times 100\%$$

Covariates were added to the model when they changed the OR by at least 5% or were statistically significant ($P < 0.05$). Thereafter, the main analysis was stratified by the type of vaccine (mRNA vs viral vector) and time from the last dose (14–179 or ≥180 days). This cut-off was selected according to the methodology used by Thompson et al.[11] and because 180 days is the recommended interval for inoculation with a booster after the primary series.[18]

The analysis was repeated for severe outcomes (hospitalisation over 24 h, I/ICU admission and/or death). Data analysis and graphical representation were conducted using the R software, Vienna, Austria (version 4.1.3 for Rstudio Build 461) with additional packages: 'readxl', 'xlsx', 'lubridate', 'dplyr', 'summarytools', 'car', 'splines', 'ggplot2', and 'ggpubr'.

The goodness of fit of the logistic regression models was assessed using the Hosmer–Lemeshow test instead of indicating a pseudo-R^2 as it does not have a clear interpretation.[19]

Possible interactions were evaluated between age and group of municipalities of residence in both models, and between age and extreme vulnerability status in the severe disease model. The likelihood ratio test was used to search for interactions.

This study included 1059 individuals (522 cases and 537 controls) with a median age of 56 years and 58% were women. Participant characteristics and eligibility criteria are shown in Table 1 and Fig. 1, respectively.

Results

Descriptive statistics and characteristics

The majority of study population were vaccinated with at least two doses of COVID-19 vaccine (89%), comparable to the national vaccine coverage during the study period.[15] In addition, most participants completed their primary scheme with mRNA vaccines, mainly Comirnaty (75%); among those administered with a booster, the last dose was an mRNA vaccine. Among the test-positive cases, 81 (16%) were hospitalised for more than 24 h; 12 (2%) were admitted to the I/ICU; and 18 (3%) died.

Effectiveness against symptomatic infection – crude model

The crude effectiveness of the primary vaccination scheme was 38% (95% confidence interval [CI]: 3%, 61%) between 14 and 179 days after the last vaccination, and 29% (95% CI: −17%, 57%) ≥180 days after the last vaccination (see Fig. 2A). The crude effectiveness of the primary scheme followed by a booster was 78% (95% CI: 65%, 86%).

Effectiveness against symptomatic infection – adjusted model

The absolute effectiveness of the primary vaccination series against symptomatic infection was lower ≥180 days after the last dose (34%; 95% CI: −12%, 61%) than between 14 and 179 days after the last dose (50%; 95% CI: 18%, 69%). Meanwhile, the absolute effectiveness of booster vaccination was higher (81%; 95% CI: 68%, 89%) than that of complete vaccination, as represented in Fig. 2A. The model was adjusted for age (as a continuous variable) using a cubic spline, for the group of municipalities of residence and the calendar month of testing, as shown in Table 2. Sex was not a confounder in any model in this study and extreme vulnerability status did not prove to be a confounder in this specific model.

Compared with the effectiveness of the primary vaccination scheme at 14–179 days after the last dose, the relative effectiveness of the booster vaccination was 63% (95% CI: 42%, 76%; $P < 0.001$). The relative effectiveness of booster vaccination was higher (71%; 95% CI: 57%, 81%; $P < 0.001$) than the effectiveness of the primary vaccination scheme ≥180 days after the last dose.

Type of vaccine

The effectiveness of the primary series against symptomatic infection was 56% (95% CI: 24%, 74%) and 41% (95% CI: −13%, 70%) between 14 and 179 days after the last dose of mRNA and viral vector vaccines, respectively. At ≥180 days after the last dose, the effectiveness of mRNA and viral vector vaccines was 40% (95% CI: −6%, 66%) and 33% (95% CI: −60%, 74%), respectively. The vaccine effectiveness stratified by the type of vaccine is presented in Fig. 2B.

The effectiveness of three doses of mRNA and viral vector vaccines and a booster dose with mRNA vaccine was 84% (95% CI: 70%, 92%) and 74% (95% CI: 30%, 90%), respectively. This model was adjusted for age (as a continuous variable) using a cubic spline, for the group of municipalities of residence and the calendar month of testing.

Table 1
Clinical and demographic characteristics of the study participants during the fifth pandemic wave dominated by the Omicron variant (1 November 2021 to 2 March 2022).

Characteristics	Total ($N = 1059$)	Cases ($n = 522$)	Controls ($n = 537$)	*P*-value
Age group in years [(n (%)]				
<65	622 (58.7%)	363 (69.5%)	259 (48.2%)	<0.001[a]
≥65	437 (41.3%)	159 (30.5%)	278 (51.8%)	
Age in years [median year (IQR)]	56 (37–78)	47 (33–71)	66 (44–81)	<0.001[a]
Sex [(n (%)]				
Male	441 (41.6%)	216 (41.4%)	225 (41.9%)	0.913
Female	618 (58.4%)	306 (58.6%)	312 (58.1%)	
Vaccination status [(n (%)]				
Unvaccinated	107 (10.1%)	72 (13.8%)	32 (6.5%)	<0.001[a]
Partially vaccinated	22 (2.1%)	14 (2.7%)	8 (1.5%)	
Fully vaccinated	563 (53.2%)	322 (61.7%)	241 (44.9%)	
Booster	367 (34.7%)	114 (45.4%)	253 (47.1%)	
Extremely vulnerable status [(n (%)]				
Yes	125 (11.8%)	54 (10.3%)	71 (13.2%)	0.175
No	934 (88.3%)	468 (89.7%)	466 (86.8%)	
Hospitalisation for >24 h [(n (%)]				
Yes	199 (18.8%)	81 (15.5%)	118 (22.0%)	0.009[a]
No	860 (81.2%)	441 (84.5%)	419 (78.0%)	
Test type [(n (%)]				
rRT-PCR	1042 (98.4%)	511 (97.9%)	531 (98.9%)	0.321
Xpress RT-PCR	4 (0.4%)	2 (0.4%)	2 (0.4%)	
Antigenic	13 (1.2%)	9 (1.7%)	4 (0.7%)	
Type of vaccine, if vaccinated [(n (%)]				
1st dose				
Comirnaty	633 (66.5%)	296 (65.8%)	337 (67.1%)	0.027[a]
Spikevax	129 (13.6%)	52 (11.6%)	77 (15.3%)	
Vaxzevria	106 (11.1%)	45 (10.0%)	61 (12.2%)	
Janssen	66 (6.9%)	41 (9.1%)	25 (5.0%)	
Missing	18 (1.9%)	16 (3.6%)	2 (0.4%)	
2nd dose				
Comirnaty	628 (72.0%)	290 (72.5%)	338 (71.6%)	
Spikevax	122 (14.0%)	49 (12.2%)	73 (15.5%)	
Vaxzevria	105 (12.0%)	45 (11.2%)	60 (12.7%)	0.428
Missing	17 (1.9%)	16 (4.0%)	1 (0.2%)	
3rd dose				
Comirnaty	344 (93.5%)	102 (88.7%)	242 (95.7%)	
Spikevax	21 (5.7%)	10 (8.7%)	11 (4.3%)	
Missing	3 (0.8%)	3 (2.6%)	0 (0%)	0.136
I/ICU admission [(n (%)]				
Yes	17 (1.6%)	12 (2.3%)	5 (0.9%)	0.127
No	1042 (98.4%)	510 (97.7%)	532 (99.1%)	
Residence [(n (%)]				
Vale do Minho	128 (12.1%)	39 (7.5%)	89 (16.6%)	<0.001[a]
Vale do Lima	931 (87.9%)	483 (92.5%)	448 (83.4%)	
Time between the date of the last dose and date of symptoms, if vaccinated [median no. of days (IQR)]				
Primary series	160 (134–195.5)	163.5 (138.3–196.8)	154 (123–193)	0.013[a]
Booster	57 (36.5–83)	62.5 (37.3–80.8)	56 (36–84)	0.576

The Mann–Whitney test was used for the continuous variables (age and time) and the chi-squared or Fisher's exact test for the categorical variables. IQR, interquartile range; I/ICU, intermediate or intensive care unit.
[a] Statistical significance for $\alpha = 0.05$.

Waning of effectiveness

Vaccine effectiveness decreased over time (Fig. 2C). The point estimate of the effectiveness of the primary series against symptomatic infection peaked at 85% (95% CI: 56%, 95%) between 14 and 90 days after the last inoculation and decreased to 66% (95% CI: 22%, 85%) between 91 and 120 days, 43% (95% CI: 2%, 67%) between 121 and 179 days, and 34% (95% CI: −30%, 56%) after ≥180 days (Fig. 2C).

The point estimate of the effectiveness of a booster was 83% (95% CI: 67%, 92%) between 14 and 42 days, remained stable (83%; 95% CI: 65%, 92%) between 43 and 70 days, and decreased after >70 days (69%; 95% CI: 23%, 88%). This model was adjusted for age (as a continuous variable) using a cubic spline, the group of municipalities of residence and the calendar month of testing.

Vaccine effectiveness for severe outcomes

The effectiveness of the primary vaccination series against severe outcomes was 83% (95% CI: 61%, 93%), while that with a booster was 90% (95% CI: 71%, 97%). Stratification showed an effectiveness of 87% (95% CI: 60%, 96%) between 14 and 179 days after the last dose and 81% (95% CI: 51%, 92%) ≥180 days after the last dose. This model was adjusted for age (as a continuous variable), extreme vulnerability status, the group of municipalities of residence and the calendar month of testing (Table 3).

The Hosmer–Lemeshow test yielded *P*-values of 0.195 and 0.633 for the symptomatic and severe disease models, respectively. Therefore, this study could not exclude the hypothesis of the models having a good fit.

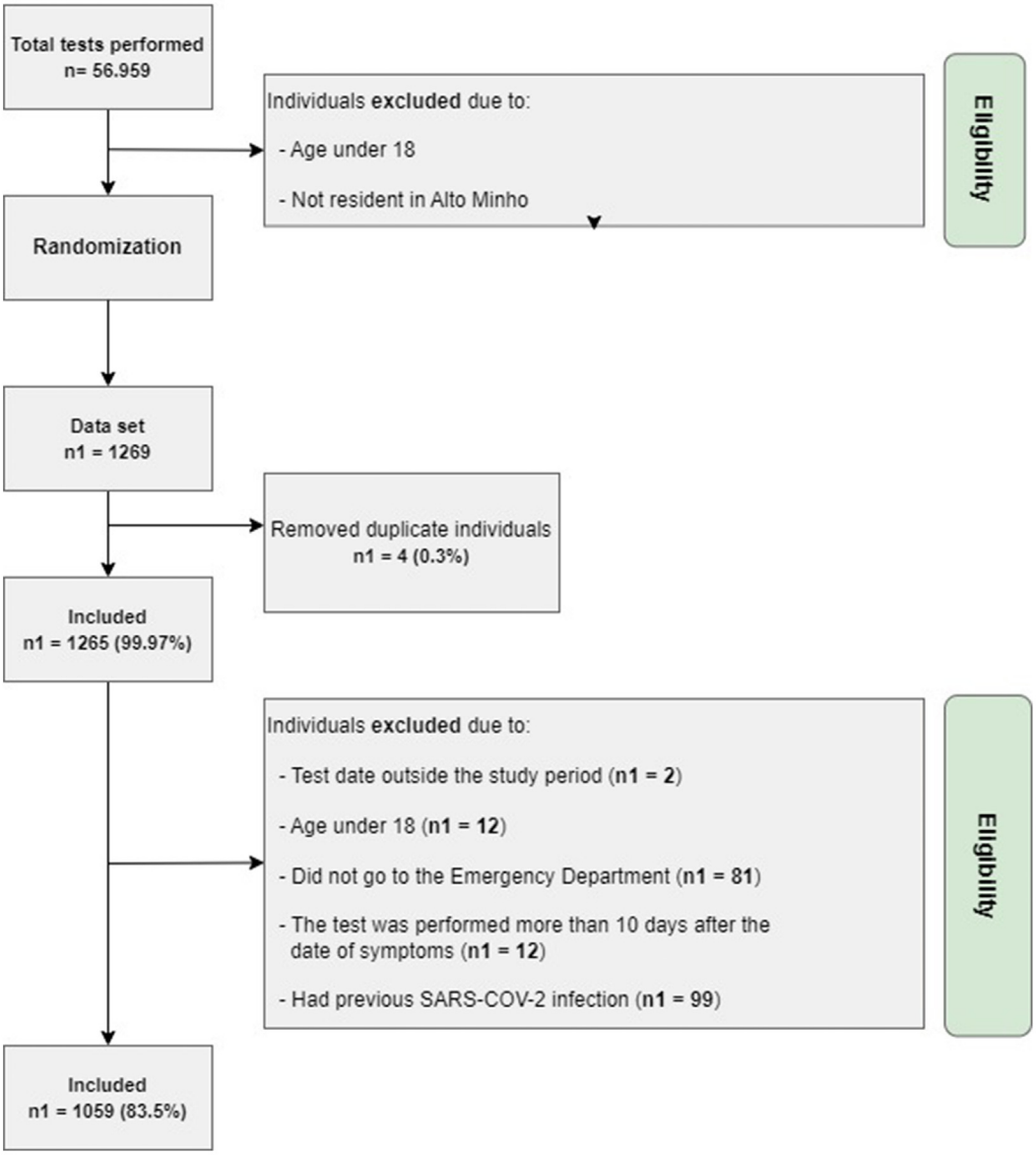

Fig. 1. Flowchart of the included and excluded individuals. A sample was randomly selected from the total tests performed between 1 June 2021 and 2 March 2022 ($N = 56{,}959$).

A statistically significant interaction was found in the severe disease model between age and the group of municipalities of residence (Table 3).

The magnitude of missing data was low (9%). Most missing data were observed on the date of symptom onset (7%); missing observations were completed with the test date. As there were a few missing observations, this was unlikely to impact the results.

Discussion

In this analysis, the absolute effectiveness of a booster was superior to that of the primary series and was even higher when the last inoculation was ≥180 days. In the study population who completed the primary series more than six months earlier, the booster prevented 71 of 100 symptomatic infections that would have occurred in the absence of a booster.

The mRNA vaccines (BNT162b2 and mRNA-1273) provided superior protection against symptomatic disease over the viral vector vaccines, although the result was not statistically significant.

Having an extremely vulnerable status was considered a confounder in the model of severe outcomes. Table 3 shows that being extremely vulnerable (as a result of immunosuppression and/or severe respiratory diseases, among other criteria described elsewhere)[16] is a risk factor for severe disease.

The residents in Vale do Minho showed a reduced risk of infection (adjusted OR = 0.50) but an increased risk of severe disease (adjusted OR = 3.54) compared with the residents in Vale do Lima. Vale do Minho is a more rural part of Alto Minho and is inhabited by older people who are usually less exposed to the virus but who can develop complications and more severe diseases. However, as the model was adjusted for age, an external factor may explain these differences, such as the access to health care, which may be compromised for residents in Vale do Minho, as the two hospitals in Alto Minho are located in Vale do Lima.

Despite the known characteristics of immunological evasion of the Omicron variant, the results of the present study show that vaccine effectiveness increased after booster vaccination, which is consistent with results from other studies.[9,20] Furthermore,

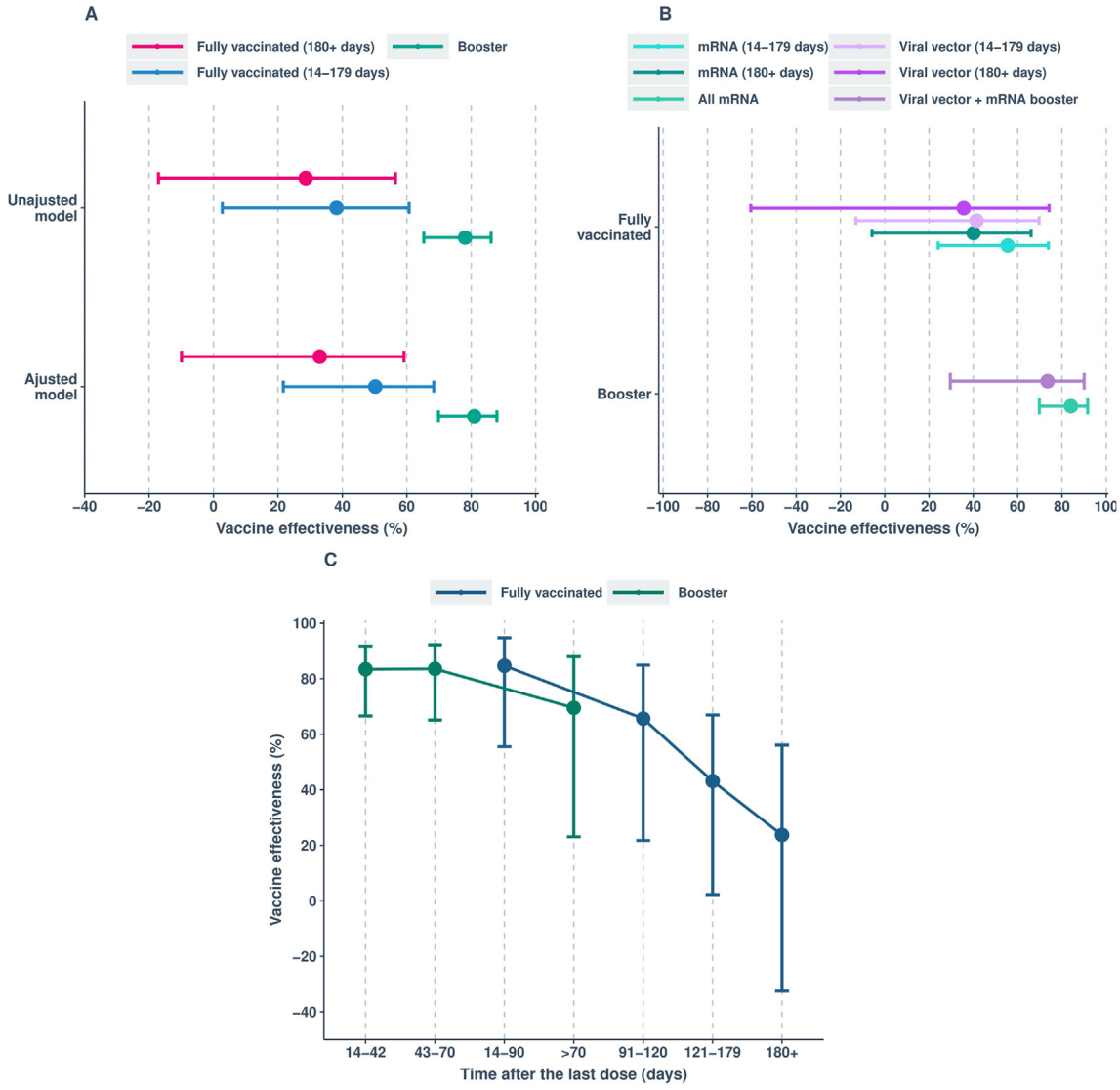

Fig. 2. Scree plot of the vaccine effectiveness for symptomatic infection in the fifth pandemic wave: A – Fully vaccinated (i.e. primary series only) vs. booster, stratified by time since the last vaccine dose. B – Fully vaccinated (i.e. primary series only) vs. primary series + booster, stratified by time since the last dose and type of vaccine (mRNA vs viral vector vaccines). C – Waning of vaccine effectiveness stratified by time after the last dose. Models adjusted for age and the group of municipalities of residence.

immunological studies suggest that there is an increase in immune response after the second dose, including a rise in the concentration and adaptation of the anti-receptor binding domain, specific for memory B cells, which confers biological plausibility for a higher vaccine effectiveness after booster vaccination, even with a highly divergent variant such as Omicron.[21–24]

The present study results also add to the accumulating evidence of the waning of vaccine protection over time for the primary series.[24,25] The effectiveness decreased to less than 50% between the third and sixth months after the last dose, so this may be the most appropriate time for booster administration.

The present study suggests that COVID-19 is less likely to result in hospitalisation, I/ICU admission and/or death in patients inoculated with a booster than in those who received only the primary scheme.

Strengths and limitations

The present study design has the following substantial strengths: (1) the cases and controls were recruited from the same healthcare unit and resided in the same geographical area, reducing bias due to risk variation according to locality;[15] (2) the cases and controls all sought care for a defined set of symptoms, which lowers the probability of health-seeking bias, an advantage of the study compared with traditional case–control and cohort studies;[15,26,27] (3) the vaccination status is usually recorded before knowing the test result, avoiding a potential differential misclassification bias;[15] and (4) the Local Health Unit of Alto Minho provided resident-level demographic and clinical data, allowing the study to analyse more detailed and complete data.

Some weaknesses of the study must also be considered, mainly due to its observational nature. There may be confounding when the vaccination status is associated with the risk of SARS-CoV-2 exposure. If, for instance, individuals who choose not to be vaccinated are also those who do not adhere to individual protective measures, this may lead to an overestimation of the vaccine effectiveness. Meanwhile, vaccinated individuals may exhibit more risky behaviours by believing they are protected, resulting in an underestimation of the vaccine effectiveness.[15] The sensitivity of PCR tests is not 100%, which may have led to the misclassification of

Table 2
Multivariable logistic regression model for symptomatic infection.

Variables	Symptomatic infection model		
	OR	95% confidence interval	*P*-value
Vaccination status			
Unvaccinated	Ref.	Ref.	Ref.
Fully vaccinated (14–179 days)	0.50	(0.31–0.82)	0.006[a]
Fully vaccinated (≥180 days)	0.66	(0.39–1.12)	0.123
Booster	0.19	(0.11–0.32)	<0.001[a]
Age (cubic spline with 3 DF)			
Component 1	0.63	(0.33–1.22)	0.169
Component 2	0.51	(0.15–1.74)	0.281
Component 3	0.28	(0.14–0.55)	<0.001[a]
Residence			
Vale do Lima	Ref.	Ref.	Ref.
Vale do Minho	0.52	(0.33–0.81)	0.003[a]
Month			
November	Ref.	Ref.	Ref.
December	1.25	(0.81–1.94)	0.317
January	3.51	(2.15–5.71)	<0.001
February	3.00	(1.79–5.05)	<0.001
March[b]	<0.001	(0–inf)	0.973

OR: odds ratio. Ref: reference.
[a] Statistical significance for $\alpha = 0.05$.
[b] Data were only analysed until March 2; therefore, we only had few observations in March, all of which were controls, rendering the confidence interval for this month to be wide.

Table 3
Multivariable logistic regression model for severe disease.

Variables	Severe disease model		
	OR	95% confidence interval	*P*-value
Vaccination status			
Unvaccinated	Ref.	Ref.	Ref.
Fully vaccinated (14–179 days)	0.13	(0.05–0.40)	<0.001[a]
Fully vaccinated (≥180 days)	0.19	(0.08–0.49)	<0.001[a]
Booster	0.10	(0.04–0.30)	<0.001[a]
Age	1.08	(1.06–1.10)	<0.001[a]
Group of municipalities of residence			
Vale do Lima	Ref.	Ref.	Ref.
Vale do Minho	<0.001	(0.001–25)	0.140
Group of municipalities of residence by age			
Vale do Lima	Ref.	Ref.	Ref.
Vale do Minho	1.18	(1.03–1.51)	0.008[a]
Extremely vulnerable status			
No	Ref.	Ref.	Ref.
Yes	4.49	(2.00–10.13)	<0.001[a]
Month			
November	Ref.	Ref.	Ref.
December	0.25	(0.09–0.70)	0.008[a]
January	0.37	(0.13–1.08)	0.069
February	0.34	(0.11–1.03)	0.056

OR: odds ratio; Ref: reference.
[a] Statistical significance for $\alpha = 0.05$.

cases in either of the controls and consequently may have attenuated the vaccine effectiveness estimates. In addition, the sample size precluded distinguishing the vaccine effectiveness among the more severe outcomes of COVID-19 – ICU admission and death. It was also difficult to directly measure the vaccine effectiveness against specific virus variants owing to the low proportion of genotyped cases. Nevertheless, this study analysed periods when different variants were dominant; thus, the study had an approximated vaccine effectiveness against these variants indirectly.

The present study was conducted primarily in the context of the Omicron sublineage BA.1. The sublineage BA.2 became dominant in the last week of the study period, and its prevalence increased in many areas of the world, indicating a likely competing advantage compared with BA.1. Nevertheless, recent evidence suggests that this advantage is related mainly to increasing transmissibility rather than to a higher immunity evasion.[28–30] Therefore, theoretically, the present study results would have been the same in the context of BA.2.[31]

The present results may not be representative of the wider general population, including people who are less prone to seek medical care in case of symptoms (e.g. ethnic minorities or people living in deprived areas). Although many relevant confounders were controlled in the models of vaccine effectiveness, residual or unmeasured confounding may have occurred.

The present study was restricted to the analysis of the first booster, as the second booster was approved in Portugal only after the study period. Future studies on the second booster are necessary.

Conclusions

This study has shown that vaccine effectiveness increases after booster administration. The optimal time for booster administration is between 3 and 6 months after completion of the primary cycle as this is the time when vaccine effectiveness decreases to less than 50%.

Author statements

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Ethical approval

The Ethics Committee of the Local Health Unit of Alto Minho (ULSAM) approved the protocol of this study with the reference number 05/2022. We followed STROBE guidelines, as can be seen in the supplementary material. The ethical principles of human medical research contained in the Declaration of Helsinki and national legislation were respected. The data collected were anonymised, guaranteeing the necessary confidentiality of the information collected. In addition, the principal investigator and her supervisors are subjected to medical confidentiality according to the Code of Ethics of the Portuguese Medical Association.

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Competing interests

None declared.

Author contributions

Conceptualisation, C.B., A.A. and R.D.; methodology, C.B., A.A., M.P. and F.A.; writing – original draft preparation, C.B.; writing – review and editing, all authors; supervision, R.D., M.P., A.A. and L.S. All authors have read and agreed to the published version of the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.puhe.2023.02.015.

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