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Vaccine 41 (2023) 2343–2348

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Effectiveness of full (booster) COVID-19 vaccination against severe outcomes and work absenteeism in hospitalized patients with COVID-19 during the Delta and Omicron waves in Greece

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ARTICLE INFO

Article history:
Received 3 December 2022
Received in revised form 11 January 2023
Accepted 28 January 2023
Available online 2 February 2023

Keywords:
COVID-19
Booster
Vaccine effectiveness
Hospitalization
Absenteeism

ABSTRACT

Aim: We estimated vaccine effectiveness (VE) of full (booster) vaccination against severe outcomes in hospitalized COVID-19 patients during the Delta and Omicron waves.
Methods: The study extended from November 15, 2021 to April 17, 2022. Full vaccination was defined as a primary vaccination plus a booster ≥ 6 months later.
Results: We studied 1138 patients (mean age: 66.6 years), of whom 826 (72.6 %) had ≥ 1 comorbidity. Of the 1138 patients, 75 (6.6 %) were admitted to intensive care unit (ICU), 64 (5.6 %) received mechanical ventilation, and 172 (15.1 %) died. There were 386 (33.9 %) fully vaccinated, 172 (15.1 %) partially vaccinated, and 580 (51 %) unvaccinated patients. Unvaccinated patients were absent from work for longer periods compared to partially or fully vaccinated patients (mean absence of 20.1 days versus 12.3 and 17.3 days, respectively; p-value = 0.03). Compared to unvaccinated patients, fully vaccinated patients were less likely to be admitted to ICU [adjusted relative risk (ARR: 0.49; 95 % CI: 0.29–0.84)], mechanically ventilated (ARR: 0.43; 95 % CI: 0.23–0.80), and die (ARR: 0.57; 95 % CI: 0.42–0.78), while they were hospitalized for significantly shorter periods (ARR: 0.79; 95 % CI: 0.70–0.89). The adjusted full VE was 48.8 % (95 % CI: 42.7 %-54.9 %) against ICU admission, 55.4 % (95 % CI: 52.0 %-56.2 %) against mechanical ventilation, and 22.6 % (95 % CI: 7.4 %-34.8 %) against death. For patients with ≥ 3 comorbidities, VE was 56.2 % (95 % CI: 43.9 %-67.1 %) against ICU admission, 60.2 % (95 % CI: 53.7 %-65.4 %) against mechanical ventilation, and 43.9 % (95 % CI: 19.9 %-59.7 %) against death.
Conclusions: Full (booster) COVID-19 vaccination conferred protection against severe outcomes, prolonged hospitalization, and prolonged work absenteeism.

1. Introduction

Despite the successful implementation of massive vaccination campaigns during the past two years, COVID-19 remains a leading

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https://doi.org/10.1016/j.vaccine.2023.01.067
0264-410X/

cause of hospitalization and mortality globally that can be prevented by vaccination [1]. The lasting prevalence of adverse COVID-19 outcomes can be mostly attributed to the waning vaccine-derived immunity, the emergence of highly transmissible SARS-CoV-2 subvariants with immune-escape capacity, but also to the fact that several individuals remain unvaccinated for various reasons [2–7]. Starting in September 2021, booster vaccine doses have been highly recommended in many countries including Greece, particularly for persons with comorbidities predisposing to severe COVID-19 outcomes, as well as to persons at high-risk for exposure to SARS-CoV-2 [3,8–10]. Early evidence from large population-based studies showed that vaccine effectiveness (VE) was 55.5 % against any symptomatic Omicron SARS-CoV-2 infection as early as two to three weeks after a booster mRNA vaccine dose, while VE against severe or fatal COVID-19 surpassed 90 % [11]. Previous work demonstrated that full (booster) COVID-19 vaccination of healthcare personnel (HCP) in the context of a mandatory vaccination policy in Greece significantly reduced the duration of HCP absenteeism during a period dominated by the Omicron variant [12]. Moreover, our study indicated that a history of less than four months since the last vaccine dose significantly protected HCP against the onset of COVID-19, febrile episode, influenza-like illness, and prolonged absenteeism, irrespective of full or partial vaccination status [12].

The aim of this study was to estimate the association of severe outcomes (admission to ICU, invasive mechanical ventilation, and/or death), duration of hospitalization, and work absenteeism with full (booster) COVID-19 vaccination in hospitalized COVID-19 patients during the Delta and Omicron waves in Greece and the VE of a booster dose compared to unvaccinated hospitalized COVID-19 patients. Our findings may guide COVID-19 vaccination policies and provide evidence to raise confidence on vaccination benefits.

2. Methods

2.1. Study setting

We conducted a prospective, observational study in five tertiary-care hospitals across Greece from November 15, 2021 (week 46/2021) to April 17, 2022 (week 15/2022). In particular, the following hospitals participated in the study: Laikon General Hospital (Athens), Sotiria General Hospital (Athens), Korgialeneio-Benakeio Red Cross Hospital (Athens), 251 Hellenic Air Force General Hospital (a military hospital in Athens), and University Hospital of Alexandroupolis (in Alexandroupolis). At that time, the Delta (B.1.617.2) variant prevailed until week 50/2021 and co-circulated with the Omicron (B.1.1.529) variant in weeks 51/2021 and 52/2021, while the Omicron variant dominated from week 01/2022 onwards [13].

2.2. Study population

Adult patients consecutively admitted with COVID-19 were included in the study. Exclusion criteria were being younger than 17 years of age, no laboratory-confirmed COVID-19, asymptomatic SARS-CoV-2 infection, and healthcare-associated COVID-19.

2.3. Data collection

The following data were collected prospectively per COVID-19 case: demographic characteristics, comorbidities (chronic cardiovascular disease, diabetes mellitus, immunosupression, malignancy, obesity, chronic neuromuscular disorder, chronic pulmonary disease, chronic renal disease), history of COVID-19 vaccination (including brand name of vaccine, number of doses, and date of last dose), history of seasonal influenza vaccination, date of onset of COVID-19-asssociated symptoms, date of COVID-19 diagnosis, healthcare-associated infections (blood stream infections, urinary tract infections, lower respiratory tract infections, gastrointestinal infections, other), admission to intensive care unit (ICU), mechanical ventilation, duration of hospitalization, death (in-hospital mortality), and duration of absenteeism from work (if any). Data about COVID-19 vaccination were retrieved from the national COVID-19 vaccination registry. The data were entered in one excel sheet per week, which was forwarded for data entry in the central database upon completion of the follow-up of each week's COVID-19 cases.

2.4. Definitions

A COVID-19 case was defined as a patient with compatible symptoms and a positive SARS-CoV-2 reverse transcription-polymerase chain reaction (RT-PCR) and/or rapid antigen detection test (RADT). Full COVID-19 vaccination was defined as a complete primary series with BNT162b2 (Comirnaty; 2 doses), mRNA-1273 (Spikevax; 2 doses), ChAdOx1-S (Vaxzevria; 2 doses), AD26.COV2.S (Janssen; 1 dose), or NVX-CoV2373 (Novavax; 2 doses), followed by a booster dose at least six months after the primary series. Partial COVID-19 vaccination was defined as a history of COVID-19 vaccination not fulfilling the criteria for full COVID-19 vaccination (e.g. incomplete primary series, complete primary series not followed by a booster dose six months later). Adverse outcomes were defined as admission to ICU, invasive mechanical ventilation, and/or death. Absenteeism was defined as absence of a patient from work because of COVID-19.

2.5. Statistical analysis

We initially conducted a descriptive analysis to characterize our study population overall and further stratified by COVID-19 vaccination status (no vaccination, partial vaccination, or full vaccination). Differences across subgroups were evaluated using chi-squared tests for categorical variables, and analysis of variance (ANOVA) or Kruskal Wallis tests for continuous variables, depending on the normality of their distribution. To estimate the association between the three adverse outcomes separately and combined (any of the three) and COVID-19 vaccination status, we conducted multivariable generalized linear regression models with modified Poisson distributions, log-link functions and robust error variances to estimate adjusted risk ratios (aRR), controlling for all factors and characteristics used in the descriptive analyses. Similarly, a negative binomial regression model was used to estimate association between duration of hospitalization and COVID-19 vaccination status, due to the skewed distribution and overdispersion. Across all regressions, hospital-fixed effects were also used to adjust for unobserved hospital-level heterogeneity. Given that the BNT162b2 mRNA vaccine was used in 80.6 % of vaccinations, vaccine brands were not considered in statistical analysis. Despite, we conducted additional regressions using only patients who received BNT162b2 mRNA vaccines to evaluate the robustness of our findings. The multivariable regression adjusted COVID-19 VE against any outcome was estimated as follows: [1 – predicted probability of outcome in vaccinated patients/predicted probability of outcome in unvaccinated patients] $\times$ 100 [14]. VE was also estimated separately by patients' number of comorbidities to assess potential variation based on pre-existing comorbidities [15]. Data were collected using Microsoft Excel and all statistical analyses were conducted using Stata version 17.0 (StataCorp, College Station, TX, USA).

2.6. Ethical issues

The protocol was approved by the Ethics Committees of the participating hospitals (approval numbers: 2218/27–01-2022, 684/27–10-2021, 43561/2021, 665/21–01-2022, 17/4003/9–12-21). The study has been conducted in full compliance with the Declaration of Helsinki.

Table 1
Characteristics of patients with COVID-19, November 15, 2021 to April 17, 2022.

Characteristic	N = 1138 (%)
Mean age, years (SD)	66.6 (17.5)
Gender	
Male	626 (55.0)
Female	512 (45.0)
At least one comorbidity	826 (72.6)
Number of comorbidities*	
One	355 (31.2)
Two	318 (27.9)
Three or more	153 (13.4)
Influenza vaccination	629 (55.3)
COVID-19 vaccination	
Full vaccination	386 (33.9)
Partial vaccination	172 (15.1)
No vaccination	580 (51.0)
Mean duration from last vaccine dose to diagnosis, days (SD)	128.9 (81.1)
Mean duration from diagnosis to admission, days (SD)	2.4 (4.6)
Mean duration of hospitalization, days (SD)	10.1 (9.4)
Admission to ICU	75 (6.6)
Mean duration in ICU, days (SD)	18.1 (14.9)
Invasive mechanical ventilation	64 (5.6)
Mean duration of mechanical ventilation, days (SD)	15.5 (15.5)
Death	172 (15.1)
Any adverse outcome	205 (18.0)
Healthcare-associated infection**	92 (8.1)

COVID-19: coronavirus disease 2019; SD: standard deviation; ICU: intensive care unit.
* chronic cardiovascular disease (450), diabetes mellitus (234), immunosupression (171), malignancy (164), obesity (151), chronic neuromuscular disorder (135), chronic pulmonary disease (121), chronic renal disease (77).
** blood stream infection (32), urinary tract infection (23), lower respiratory tract infection (20), gastrointestinal infection (8), other (9).

3. Results

During the 22-week study period, 1138 patients were consecutively admitted with COVID-19 for a mean duration of hospitalization of 10.1 [standard deviation (SD): 9.4] days (Table 1). Hospitalized patients had a mean age of 66.6 (SD: 17.5) years, and 826 (72.6 %) of them had at least one comorbidity. Of the 1138 patients, 75 (6.6 %) patients were admitted to an ICU, 64 (5.6 %) patients were on invasive mechanical ventilation, and 172 (15.1 %) died during hospitalization. Overall, 205 (18 %) of the 1138 patients had at least one adverse outcome. Of the 1138 hospitalized COVID-19 patients, 386 (33.9 %) patients were fully vaccinated, 172 (15.1 %) patients were partially vaccinated, and 580 (51 %) patients were unvaccinated. Table 2 shows the patients' characteristics stratified by COVID-19 vaccination status. Compared to partially or fully vaccinated COVID-19 patients, unvaccinated COVID-19 patients were hospitalized for significantly longer duration (mean duration of hospitalization 10.9 days versus 10.2 and 9 days, respectively; p-value < 0.001), higher rates of admission to ICU (8.6 % versus 4.7 % and 4.4 %, respectively; p-value = 0.019), higher rates of invasive mechanical ventilation (7.6 % versus 4.1 % and 3.4 %, respectively; p-value = 0.015), and higher rates of any adverse outcome (20.5 % versus 17.4 % and 14.5 %, respectively; p-value = 0.057). Similarly, among 406 employed patients, unvaccinated patients were absent from their work for significantly longer time periods compared to partially or fully vaccinated patients (20.1 days versus 12.3 and 17.3 days, respectively; p-value = 0.03). Overall, unvaccinated patients accounted for 95 out of 172 deaths in our series, compared to 28 deaths among partially vaccinated patients and 49 among fully vaccinated patients. Lastly, among 558 COVID-19 patients with a history of full or partial COVID-19 vaccination, a mean of 128.9 (SD: 81.1) days elapsed since the last vaccine dose. There were 281 (50.4 %) patients vaccinated within<128.9 days before diagnosis and 277 (49.6 %) patients vaccinated>128.9 days before. The two groups did not differ significantly in terms of rates of admission to ICU, invasive mechanical ventilation, death, and any adverse outcome, and in terms of mean duration of hospitalization, admission to ICU, invasive mechanical ventilation, and work

Table 2
Characteristics of COVID-19 patients by COVID-19 vaccination status.

Characteristic	No vaccination N = 580	Partial vaccination N = 172	Full vaccination N = 386	P-value
Mean age, years (SD)	64.0 (17.7)	69.8 (16.2)	69.2 (17.2)	<0.001
Gender				0.04
Male	298 (51.4)	99 (57.6)	229 (59.3)	
Female	282 (48.6)	73 (42.4)	157 (40.7)	
At least one comorbidity	384 (66.2)	140 (81.4)	303 (78.5)	<0.001
Number of comorbidities				<0.001
One	195 (33.6)	48 (27.9)	112 (29.0)	
Two	137 (23.6)	64 (37.2)	117 (30.3)	
Three or more	51 (8.8)	28 (16.3)	74 (19.2)	
Influenza vaccination	249 (42.9)	114 (66.3)	266 (68.9)	<0.001
Mean duration from last vaccine dose to diagnosis, days (SD)	–	170.3 (114.3)	110.5 (51.0)	<0.001
Mean duration from diagnosis to admission, days (SD)	2.6 (4.4)	2.4 (4.3)	2.1 (5.1)	0.02
Mean duration of hospitalization, days (SD)	10.9 (9.4)	10.2 (8.7)	9.0 (9.6)	<0.001
Admission to ICU	50 (8.6)	8 (4.7)	19 (4.4)	0.019
Mean duration in ICU, days (SD)	17.4 (14.8)	20.0 (17.6)	19.3 (14.5)	0.01
Invasive mechanical ventilation	44 (7.6)	7 (4.1)	13 (3.4)	0.015
Mean duration of mechanical ventilation, days (SD)	14.7 (13.9)	20.4 (20.7)	15.5 (16.5)	0.03
Death	95 (16.4)	28 (16.3)	49 (12.7)	0.264
Any adverse outcome	119 (20.5)	30 (17.4)	56 (14.5)	0.057
Healthcare-associated infection	46 (7.9)	16 (9.3)	30 (7.8)	0.814
Mean duration of absence from work, days (SD)*	20.1 (13.0)	12.3 (6.5)	17.3 (14.9)	0.03

COVID-19: coronavirus 2019; SD: standard deviation; ICU: intensive care unit.
* concerns 406 employed patients.

Table 3
Logistic regressions' estimates.

	Admission to ICU		Mechanical ventilation		Death		Adverse outcome		Duration of hospitalization	
	ARR (95 % CI)	p-value	ARR (95 % CI)	p-value	ARR (95 % CI)	p-value	ARR (95 % CI)	p-value	IRR (95 % CI)	p-value
COVID-19 vaccination										
no vaccination	ref.		ref.		ref.		ref.		ref.	
partial vaccination	0.46 (0.22–0.96)	0.037	0.47 (0.22–1.04)	0.062	0.72 (0.50–1.02)	0.066	0.62 (0.45–0.87)	0.006	0.86 (0.75–0.99)	0.03
full (booster) vaccination	0.49 (0.29–0.84)	0.009	0.43 (0.23–0.80)	0.007	0.57 (0.42–0.78)	<0.001	0.54 (0.41–0.72)	<0.001	0.79 (0.70–0.89)	<0.001
Diagnosis to admission*	1.16 (1.09–1.24)	<0.001	1.10 (1.03–1.16)	0.002	1.03 (0.99–1.07)	0.095	1.05 (1.02–1.09)	0.002	1.03 (1.01–1.04)	<0.001
Age	1.02 (1.00–1.03)	0.014	1.01 (1.00–1.03)	0.038	1.06 (1.05–1.07)	<0.001	1.05 (1.04–1.06)	<0.001	1.01 (1.00–1.01)	<0.001
Sex										
male	ref.		ref.		ref.		ref.		ref.	
female	0.88 (0.56–1.37)	0.564	0.81 (0.55–1.50)	0.708	0.94 (0.72–1.22)	0.63	0.88 (0.69–1.11)	0.276	0.89 (0.80–0.99)	0.027
Comorbidities										
none	ref.		ref.		ref.		ref.		ref.	
one	1.02 (0.56–1.85)	0.952	0.94 (0.50–1.76)	0.856	1.37 (0.89–2.12)	0.148	1.22 (0.84–1.76)	0.29	1.01 (0.89–1.15)	0.906
two	0.90 (0.48–1.69)	0.735	1.01 (0.53–1.93)	0.98	1.48 (0.94–2.33)	0.092	1.29 (0.87–1.90)	0.201	1.16 (1.00–1.36)	0.052
three or more	1.84 (0.82–3.67)	0.086	1.17 (0.48–2.86)	0.728	2.47 (1.55–3.93)	<0.001	2.10 (1.41–3.13)	<0.001	1.17 (0.98–1.39)	0.077

All regression models included hospital fixed-effects.
COVID-19: coronavirus disease 2019; ICU: intensive care unit; ARR: adjusted relative risk; IRR: incidence rate ratio; CI: CI: confidence interval; Ref: reference.
* time elapsed from diagnosis to admission (days).

absenteeism (data not shown). Table 3 shows the results of the multivariate logistic and negative binomial regression analyses. Compared to unvaccinated patients, fully vaccinated patients had lower risks of ICU admission (ARR: 0.49; 95 % CI: 0.29–0.84), of invasive mechanical ventilation (ARR: 0.43; 95 % CI: 0.23–0.80), of death (ARR: 0.57; 95 % CI: 0.42–0.78), and of having any adverse outcome overall (ARR: 0.54; 95 % CI: 0.41–0.72) during hospitalization, while the duration of their hospitalization was significantly lower (ARR: 0.79; 95 % CI: 0.70–0.89). Compared to unvaccinated patients, partially vaccinated patients had also lower risks of admission to an ICU (ARR: 0.46; 95 % CI: 0.22–0.96), of experiencing any adverse outcome (ARR: 0.62; 95 % CI: 0.45–0.87), and staying hospitalized for longer time periods (ARR: 0.86; 95 % CI: 0.75–0.99). However, compared to no vaccination, the association between partial vaccination and in-hospital mortality was not statistically significant (ARR:0.72; 95 % CI: 0.50–1.02). Beyond vaccination status, each additional year of age increased the risks of each or any adverse outcome overall and the length of hospitalization (ARR: 1.01; 95 % CI: 1.00–1.01). Similarly, patients with longer time periods from COVID-19 diagnosis to admission were at higher risk of ICU admission (ARR: 1.16; 95 % CI: 1.09–1.24), invasive mechanical ventilation (ARR: 1.10; 95 % CI: 1.03–1.16), having any adverse outcome (ARR: 1.05; 95 % CI: 1.02–1.09), and remaining hospitalized for a longer period (ARR: 1.03; 95 % CI: 1.01–1.04). Lastly, compared to patients with no comorbidity, COVID-19 patients with at least three comorbidities had a higher risk of death (ARR: 2.47; 95 % CI: 1.55–3.93) and of any adverse outcome (ARR: 2.10; 95 % CI: 1.41–3.13). Sensitivity analyses using only patients who received BNT162b2 mRNA vaccines yielded similar estimates.

Overall, the adjusted full COVID-19 VE was estimated at 48.8 % (95 % CI: 42.7 %-54.9 %) against admission to ICU, 55.4 % (95 % CI: 52.0 %-56.2 %) against invasive mechanical ventilation, 22.6 % (95 % CI: 7.4 %-34.8 %) against death, and 29.3 % (95 % CI: 18.8 %-38.4 %) against any adverse outcome. Stratified estimation of the adjusted full COVID-19 VE by number of comorbidities revealed the highest effectiveness for patients with three or more comorbidities at 56.2 % (95 % CI: 43.9 %-67.1 %) against admission to ICU, 60.2 % (95 % CI: 53.7 %-65.4 %) against invasive mechanical ventilation, 43.9 % (95 % CI: 19.9 %-59.7 %) against death, and 45.9 % (95 % CI: 29.4 %-57.9 %) against any adverse outcome.

4. Discussion

The current study aimed to estimate the association of severe outcomes and duration of hospitalization with full (booster) COVID-19 vaccination as well as COVID-19 VE among COVID-19 patients hospitalized during the Delta and Omicron waves in Greece. A significant reduction of ICU admissions, invasive mechanical ventilations, deaths, and length of hospitalization that was conferred by a booster dose was demonstrated in our study. For instance, according to national surveillance data, out of 1042 COVID-19 patients hospitalized during the first pandemic wave in Greece, 215 (20.63 %) patients were admitted to an ICU, 208 patients (19.96 %) required invasive mechanical ventilation, and 177 patients (17 %) died. At that time, 565 (53.2 %) hospitalized patients had at least one comorbidity [16]. The findings of the current study are in line with recently published data indicating that booster doses targeting the ancestral SARS-CoV-2 Wuhan variant confer significant although incomplete protection against severe COVID-19 morbidity associated with the Delta and Omicron variants, even among patients with several comorbidities [10,15,17–20]. A Canadian study found similar inverse associations of adverse hospitalization outcomes with the number of vaccine doses [21].

In our study, older patients and patients with several comorbidities were still vulnerable to severe COVID-19 morbidity.

The moderate VE of a booster dose against admission to ICU and invasive mechanical ventilation and the rather high (15.1 %) overall in-hospital mortality is partially explained by the prevalent profile of our patients (elderly with several comorbidities), which predisposes to reduced VE [22] and increased likelihood for severe outcomes [16]. During the Omicron period, advanced age and comorbidities remained great risk factors for severe COVID-19 morbidity and death even among vaccinated patients [18,23]. Nonetheless, full (booster) vaccination reduced the risk of any adverse outcome by 45.9 % among our patients with three or more comorbidities, which is of great importance and should be communicated.

In our study, a booster COVID-19 vaccine dose also significantly reduced the duration of hospitalization, consistent with a US study of hospitalized COVID-19 patients during a Delta-dominated period [24]. This may prove critical for healthcare facilities to overcome the burden of healthcare demand and hospitalizations [25], given the possibility of influenza and COVID-19 co-circulation in the next seasons [26,27] and the fact that these infections have the same high-risk groups [28]. A recent US study using a national healthcare database of 5.8 million individuals from March 1, 2020 until June 25, 2022 found that compared to no reinfection, reinfection further increased the risk for all-cause mortality, hospitalization, and sequelae in multiple organ systems mostly in the post-acute phase, regardless of vaccination status [29]. New vaccines and vaccination strategies are needed to confer high and prolonged protection. In September-October 2022, the adjuvated recombinant protein subunit vaccine NVX-CoV2373 and two bivalent mRNA vaccines containing components of the BA.4 and BA.5 Omicron sublineages were authorized for booster doses to improve protection against COVID-19 [30–32].

In our study a mean of 128 days elapsed since the last COVID-19 vaccine dose, which is in accordance with the gradual decline of protection from the fourth month after booster vaccination, as shown in real-life studies [9,11,12,19,33]. These findings should be considered in defining the optimal COVID-19 vaccination timing.

Another finding of the current study is that unvaccinated COVID-19 patients had significantly longer periods of absence from work compared to fully (boosted) or partially vaccinated COVID-19 patients. Similarly, a primary mRNA vaccine series prevented approximately-seven out of ten episodes of absenteeism among hospital-based HCP during 2020–2021 [34]. Our findings have implications for the workforce and may guide vaccination policies in essential working settings. It has been estimated that before the deployment of COVID-19 vaccines, over 20.5 million life years were lost due to COVID-19 globally, one third of which were among individuals aged < 55 years [1]. A model-based study using Northern hemisphere seasonality simulations demonstrated that COVID-19 vaccine boosters should be administered annually to all individuals who had received two vaccine doses in the past rather than targeting boosters to high-risk groups only (persons > 60 years and persons with comorbidities), and that boosters should be delivered 3–4 months ahead of peak winter [8]. Such policies are expected to prevent severe COVID-19-associated hospitalizations over the next two years [8].

The current study is potentially subject to the following limitations. First, specific anti-SARS-CoV-2 treatment was not considered in the analysis. Second, the brand name of the last vaccine dose only was considered. Nonetheless, evidence from large studies support the use of heterologous vaccine schedules [20,35,36]. Third, the small number of cases admitted to the ICU, on invasive mechanical ventilation, and those that died stratified by time elapsed since the last vaccine dose (<compared to > the mean of 128.9 days) may account for not detecting statistical significance in adverse outcomes.

In conclusion, a booster dose significantly decreased the likelihood for admission to the ICU, invasive mechanical ventilation, and death, particularly among patients with at least three comorbidities, and was associated with a significant reduction in the duration of hospitalization among COVID-19 patients during the Delta and Omicron waves in Greece. In addition, a booster dose significantly reduced work absenteeism associated with COVID-19. However, older patients and patients with several comorbidities still remain vulnerable to severe COVID-19 morbidity. Real-life studies to estimate COVID-19 VE are needed to guide long-term vaccination policies against COVID-19 and to ensure vaccination benefits for all.

Data availability

Data will be made available on request.

Declaration of Competing Interest

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

Acknowledgements

We are thankful to the Infection Control Committees of the participating hospitals for their assistance. The opinions presented in this article are those of the authors and do not necessarily represent those of their institutions.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

[1] Pifarre I, Arolas H, Acosta E, Lopez-Casasnovas G, Lo A, Nicodemo C, et al. Years of life lost to COVID-19 in 81 countries. Sci Rep 2021;11:3504.
[2] Nguyen NN, Houhamdi L, Hoang VT, Stoupan D, Fournier PE, Raoult D, et al. High rate of reinfection with the SARS-CoV-2 omicron variant. J Infect 2022;85:206–8.
[3] Shrestha LB, Foster C, Rawlinson W, Tedla N, Bull RA. Evolution of the SARS-CoV-2 omicron variants BA.1 to BA.5: implications for immune escape and transmission. Rev Med Virol 2022;32:e2381.
[4] Burckhardt RM, Dennehy JJ, Poon LLM, Saif LJ, Enquist LW. Are COVID-19 vaccine boosters needed? the science behind boosters. J Virol 2022;96: e0197321.
[5] Psaridi L, Maltezou HC, Simonidou S, Lialliou I, Athanasopoulou D, Haila Z, et al. Neutralizing antibody responses in healthcare personnel after three doses of mRNA BNT162b2 vaccine and association with baseline characteristics and past SARS-CoV-2 infection. Vaccine 2022;40:5752–6.
[6] Levin-Rector A, Firestein L, McGibbon E, Sell J, Lim S, Lee EH, et al. Reduced odds of SARS-CoV-2 reinfection after vaccination among New York City adults, July–November 2021. Clin Infect Dis 2022 May 20; ciac380. doi: 10.1093/cid/ciac380. Online ahead of print.
[7] Bianchi FP, Stefanizzi P, Germinario CA, Migliore G, Vimercati L, Martinelli A, et al. Medium-to-long-term immunogenicity of BNT162b2 mRNA COVID-19 vaccine: a retrospective cohort study. Vaccines 2022;10:417.
[8] Kelly SL, Le Rutte EA, Richter M, Penny MA, Shattock AJ. COVID-19 vaccine booster strategies in light of emerging viral variants: frequency, timing, and target groups. Infect Dis Ther 2022;11:2045–61.
[9] Ferdinands JM, Rao S, Dixon BE, Mitchell PK, DeSilva MB, Irving SA, et al. Waning of vaccine effectiveness against moderate and severe covid-19 among adults in the US from the VISION network: test negative, case-control study. BMJ 2022;379:e072141.
[10] Ioannou GN, Bohnert ASB, O' Hare AM, Boyko EJ, Maciejewski ML, Smith VA, et al. Effectiveness of mRNA COVID-19 vaccine boosters against infection, hospitalization, and death: a target trial emulation in the omicron (B.1.1.529) variant era. Ann Intern Med 2022;175:1693-706.
[11] Chemaitelly H, Ayoub HH, Al Mukdad S, Coyle P, Tang P, Yassine HM, et al. Duration of mRNA vaccine protection against SARS-CoV-2 Omicron BA.1 and BA.2 subvariants in Qatar. Nat Commun 2022;13:3082.

[12] Maltezou HC, Gamaletsou MN, Koukou DM, Giannouchos TV, Sourri F, Syrimi N, et al. Association between COVID-19 vaccination status, time elapsed since the last vaccine dose, morbidity, and absenteeism among healthcare personnel: a prospective, multicenter study. Vaccine 2022;40:7660–6.
[13] National Public Health Organization. Weekly Report of Epidemiological Surveillance of SARS-CoV-2 Infection. Available at: https://eody.gov.gr/wp-content/uploads/2022/07/covid-gr-weekly-report-2022-28.pdf (last accessed: 11 January 2023) [in Greek].
[14] Halloran ME, Struchiner CJ, Longini Jr IM. Study designs for evaluating different efficacy and effectiveness aspects of vaccines. Am J Epidemiol 1997;146:789–803.
[15] Mallah N, Pardo-Seco J, Lopez-Perez LR, Gonzalez-Perez JM, Roson B, Otero-Barros MT, et al. Effectiveness of COVID-19 vaccine booster in the general population and in subjects with comorbidities. A population-based study in Spain. Environ Res 2022;215:114252.
[16] Maltezou HC, Papadima K, Gkolfinopoulou K, Ferentinos G, Mouratidou E, Andreopoulou A, et al. Coronavirus disease 2019 pandemic in Greece, February 26 – May 3, 2020: the first wave. Travel Med Infect Dis 2021;41:102051.
[17] Modes ME, Directo MP, Melgar M, Johnson LR, Yang H, Chaudhary P, et al. Clinical characteristics and outcomes among adults hospitalized with laboratory-confirmed SARS-CoV-2 infection during periods of B.1.617.2 (Delta) and B.1.1.529 (Omicron) variant predominance — one Hospital, California, July 15–September 23, 2021, and December 21, 2021–January 27, 2022. MMWR Morb Mortal Wkly Rep 2022;71:6:217-23.
[18] O' Leary AL, Wattengel BA, Carter MT, Drye AF, Mergenhagen KA. Risk factors associated with mortality in hospitalized patients with laboratory confirmed SARS-CoV-2 infection during the period of omicron (B.1.1.529) variant predominance. Am J Infect Control 2022;6:S0196-6553(22)00664-2.
[19] Laake I, Skodvin SN, Blix K, Caspersen IH, Gjessing HK, Juvet LK, et al. Effectiveness of mRNA booster vaccination against mild, moderate, and severe COVID-19 caused by the omicron variant in a large, population-based. Norwegian cohort J Infect Dis 2022;226:1924–33.
[20] Du Y, Chen L, Shi Y. Booster COVID-19 vaccination against the SARS-CoV-2 Omicron variant: a systematic review. Hum Vaccin Immunother 2022;18:2062983.
[21] Grima AA, Murison KR, Simmons AE, Tuite AR, Fisman DN. Relative virulence of SARS-CoV-2 among vaccinated and unvaccinated individuals hospitalized with SARS-CoV-2. Clin Infect Dis 2022 May 25;ciac412. doi: 10.1093/cid/ciac412. Online ahead of print.
[22] Tenforde MW, Self WH, Zhu Y, Naioti EA, Gaglani M, Ginde AA, et al. Protection of mRNA vaccines against hospitalized COVID-19 in adults over the first year following authorization in the United States. Clin Infect Dis 2022:ciac381.
[23] Agrawal U, Bedston S, McCowan C, Oke J, Patterson L, Robertson C, et al. Severe COVID-19 outcomes after full vaccination of primary schedule and initial boosters: pooled analysis of national prospective cohort studies of 30 million individuals in England, Northern Ireland, Scotland, and Wales. Lancet 2022;400:1305–20.
[24] Wang SY, Juthani PV, Borges KA, Shallow MK, Gupta A, Price C, et al. Severe breakthrough COVID-19 cases in the SARS-CoV-2 delta (B.1.617.2) variant era. Lancet Microbe 2022;3:e4–5.
[25] Tan E, Song J, Deane AM, Plumm MP. Global impact of coronavirus disease 2019 infection requiring admission to the ICU: a systematic review and meta-analysis. Chest 2021;159:524–36.
[26] Lee SS, Viboud C, Petersen E. Understanding the rebound of influenza in the post COVID-19 pandemic period holds important clues for epidemiology and control. Int J Infect Dis 2022;122:1002–4.
[27] Lofgren E, Naumova EN, Gorski J, Naumov Y, Fefferman NH. How drivers of seasonality in respiratory infections may impact vaccine strategy: a case study in how COVID-19 may help us solve one of influenza's biggest challenges. Clin Infect Dis 2022;75(Suppl 1):S121–9.
[28] Maltezou HC, Theodoridou K, Poland G. Influenza immunization and COVID-19. Vaccine 2020;38:6078–9.
[29] Bowe B, Xie Y, Al-Aly Z. Acute and postacute sequelae associated with SARS-CoV-2 reinfection. Nat Med 2022;28:2398–405.
[30] Health PT, Galiza EP, Baxter DN, Boffito M, Browne D, Burns F, et al. Safety and efficacy of the NVX-CoV2373 coronavirus disease 2019 vaccine at completion of the placebo controlled phase of a randomized controlled trial. Clin Infect Dis 2022 Oct 10;ciac803. doi: 10.1093/cid/ciac803. Online ahead of print.
[31] COVID-19 update: Novavax vaccine authorized for booster immunization. Med Lett Drugs Ther 2022;64:e1-2.
[32] Rosenblum HG, Wallace M, Godfrey M, Roper LE, Fleming-Dutra KE, Link-Gelles R, et al. Interim recommendations from the Advisory Committee on Immunization Practices for the use of bivalent booster doses of COVID-19 vaccines – United States, October 2022. MMWR Morb Mortal Wkly Rep 2022;71:1436–41.
[33] Saade A, Cha L, Tadié E, Jurado B, Bihan A, Baron-Latouche P, et al. Delay between COVID-19 complete vaccination and SARS-CoV-2 infection among healthcare workers. Vaccine 2022;40:3159–64.
[34] Maltezou HC, Panagopoulos P, Sourri F, Giannouchos TV, Raftopoulos V, Gamaletsou MN, et al. COVID-19 vaccination significantly reduces morbidity and absenteeism among healthcare personnel: a prospective multicenter study. Vaccine 2021;39:7021–7.
[35] Starrfelt J, Danielsen AS, Buanes EA, Juvet LK, Lyngstad TM, Isaksson GØ, et al. Age and product dependent vaccine effectiveness against SARS-CoV-2 infection and hospitalisation among adults in Norway: a national cohort study, July–November 2021. BMC Med 2022;20:278.
[36] Deng J, Ma Y, Liu Q, Du M, Liu M, Liu J. Comparison of the effectiveness and safety of heterologous booster doses with homologous booster doses for SARS-CoV-2 vaccines: a systematic review and meta-analysis. Int J Environ Res Public Health 2022;19:10752.