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Primary series COVID-19 vaccine effectiveness among healthcare workers in Albania, February–December 2021

Julia E. Rubin-Smith[1,2,†], Madelyn Yiseth Rojas Castro[6,†], Iria Preza[4], Iris Hasibra[4], Jonilda Sulo[5], Albana Fico[4], Rovena Daja[4], Adela Vasili[4], Majlinda Kota[4], Alexis Schmid[1,2], Shela Sridhar[1,3], Alina Guseinova[7], Golubinka Boshevska[7], Gazmend Bejtja[7], Barbara Mühlemann[8,9], Christian Drosten[8,9], Pernille Jorgensen[7], Richard Pebody[7], Esther Kissling[6], Kathryn E. Lafond[10], Mark A. Katz[7], Silvia Bino[4,*]

[1] *Global Health Program, Boston Children's Hospital, Boston, MA, USA*
[2] *Division of Emergency Medicine, Boston Children's Hospital, Boston, MA, USA*
[3] *Department of Global Health Equity, Brigham and Women's Hospital, Boston, MA, USA*
[4] *Institute of Public Health, Tirana, Albania*
[5] *Southeast European Centre for Surveillance and Control of Infectious Disease, Tirana, Albania*
[6] *Epiconcept, Paris, France*
[7] *World Health Organization Regional Office for Europe, Copenhagen, Denmark*
[8] *Institute of Virology, Charité–Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin, Humboldt – Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany*
[9] *German Centre for Infection Research, Partner Site Charité, Berlin, Germany*
[10] *Influenza Division, US Centers for Disease Control and Prevention, Atlanta, GA, USA*

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ABSTRACT

Background: Healthcare workers have experienced high rates of morbidity and mortality from coronavirus disease 2019 (COVID-19).

Methods: A prospective cohort study was conducted in three Albanian hospitals between 19 February and 14 December 2021. All participants underwent polymerase chain reaction (PCR) and serological testing at enrolment, regular serology throughout, and PCR testing when symptomatic.

Vaccine effectiveness (VE) against COVID-19 and against all severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infections (symptomatic or asymptomatic) was estimated. VE was estimated using a Cox regression model, with vaccination status as a time-varying variable.

Findings: In total, 1504 HCWs were enrolled in this study; 70% had evidence of prior SARS-CoV-2 infection. VE was 65.1% [95% confidence interval (CI) 37.7–80.5] against COVID-19, 58.2% (95% CI 15.7–79.3) among participants without prior SARS-CoV-2 infection, and 73.6% (95% CI 24.3–90.8) among participants with prior SARS-CoV-2 infection. For BNT162b2 alone, VE was 69.5% (95% CI 44.5–83.2). During the period when the Delta variant was predominant, VE was 67.1% (95% CI 38.3–82.5). VE against SARS-CoV-2 infection for the full study period was 36.9% (95% CI 15.8–52.7).

Interpretation: This study found moderate primary series VE against COVID-19 among healthcare workers in Albania. These results support the continued promotion of COVID-19 vaccination in Albania, and highlight the benefits of vaccination in populations with high levels of prior infection.

Introduction

Healthcare workers (HCWs) are at high risk for occupational exposures to infectious diseases, and have experienced high rates of morbidity during the coronavirus disease 2019 (COVID-19) pandemic [1–3]. They also pose a risk of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) transmission to hospitalized patients who are often at high risk of serious COVID-19 outcomes [4].

Robust mass immunization programmes, among other public health measures employed to mitigate the global impact of COVID-19, reduce

* Corresponding author at: Institute of Public Health, Alexander Moisiu treet. N. 80, Tirana, Albania.
E-mail address: silviabino@gmail.com (S. Bino).
† These authors contributed equally.

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both morbidity and mortality [5,6]. Since late 2020 when global vaccine distribution began, more than 13.3 billion COVID-19 vaccine doses have been administered worldwide [7]. Vaccine coverage in high-income countries (HICs) has far outpaced that in low- and middle-income countries (LMICs): in the World Health Organization (WHO) European Region, as of 21 March 2023, primary series vaccine coverage was 73.7% in HICs compared with 55.6% in upper middle-income countries and 42.0% in lower middle-income countries [8].

Similar disparities have emerged in evaluations of vaccine effectiveness (VE). To date, numerous observational VE studies have been conducted in HICs [9,10], but few have been published on VE in LMICs, and VE has not been evaluated in middle-income countries in the WHO European Region. Vaccine uptake and VE may be different in LMICs given differences in population age structures, comorbidities, and logistic capacity (such as cold chain integrity, vaccine transport, and delivery) [11].

In Albania, an upper middle-income country with a population of 2.9 million people, COVID-19 vaccination began on 11 January 2021 using the BNT162b2 (Comirnaty, Pfizer–BioNTech) vaccine. Initially, older people, nursing home residents, and HCWs were prioritized for vaccination [12]. This prospective cohort study was conducted in order to evaluate VE of the COVID-19 vaccine in a frequently exposed population prioritized for early vaccination (HCWs) in Albania.

Methods

Study design

This prospective cohort study was conducted to evaluate primary series COVID-19 VE against SARS-CoV-2 infection (both asymptomatic and symptomatic) among HCWs in three hospitals in Albania. The design and analysis were guided by the WHO/Europe VE guidance document [11], and the study was conducted within the framework of WHO's Unity platform [13]. Study implementation was conducted by the Albania Institute of Public Health.

Data collection and management

In February 2021, all HCWs at Tirana University Hospital, Durrës Regional Hospital and Fier Regional Hospital were invited to enrol in the study, regardless of their hospital role, prior infection status or their intention to receive the COVID-19 vaccine. These three large public hospitals represent three of the major metropolitan areas in the country. Enrolment was voluntary and all HCWs in the study who received COVID-19 vaccines did so through the national vaccine campaign led by the Ministry of Health.

At enrolment, participants completed a questionnaire that included demographics and health status; hospital role, including engagement in direct patient care; and COVID-19 and influenza vaccination history, as described previously [14]. In addition, at enrolment, each participant provided a blood sample for serological testing, and a respiratory sample for SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR) testing, regardless of whether or not they had symptoms.

Following enrolment, participants completed a weekly symptom questionnaire, administered by study personnel; participants who reported one or more symptoms included in the Albanian Ministry of Health COVID-19 case definition [14] were tested for SARS-CoV-2 by PCR. PCR-positive samples were sent to the Institute of Virology – Charité (Berlin, Germany) where they underwent genomic sequencing.

In order to identify tests performed outside of the study, study staff monitored the Albania National SARS-CoV-2 testing database. Participants who tested positive for SARS-CoV-2 at any time during the study period were administered a follow-up questionnaire 30 days after their positive test, which included questions about symptoms, need for hospitalization, and time to resolution of symptoms [14]. All study data were entered securely and stored in REDCap (Research Electronic Data Capture, Vanderbilt University, Nashville, TN, USA) [15].

Serology

Phlebotomists collected serological specimens from participants at enrolment, and subsequently at 3-month intervals [14]. Enrolment serological samples were tested with WANTAI SARS-CoV-2 Ab enzyme-linked immunosorbent assay (WANTAI BioPharm, Beijing, China), which targets SARS-CoV-2 anti-spike protein. All serological samples were also tested with Platelia SARS-CoV-2 total antibody assay (Bio-Rad Laboratories, Hercules, CA, USA) [16,17], which measures total anti-nucleocapsid antibody and therefore can be used to identify SARS-CoV-2 infections in individuals who have received mRNA and viral vector vaccines. For both serological assays, cut-off values were determined according to the package insert. Seroconversion was defined as a positive serological result (a value above the manufacturer-determined cut-off) in a participant whose most recent serology was negative. Of the 46 participants who had a PCR-confirmed infection during the analysis period, had a negative anti-nucleocapsid antibody prior to the infection and had serology collected after their infection, 42 seroconverted (91%). The median number of days between the date of PCR-confirmed infection and serological collection was 73 [interquartile range (IQR) 39–91] days.

Vaccine effectiveness analysis

For the primary outcome, primary series VE was measured against COVID-19. Cases of COVID-19 were defined as a positive PCR result in a symptomatic participant with symptom onset between 14 days before and 4 days after PCR. As a secondary analysis, primary series VE was measured against symptomatic or asymptomatic SARS-CoV-2 infection, measured by a combined outcome of PCR-confirmed SARS-CoV-2 and/or seroconversion, defined as a positive anti-nucleocapsid antibody test in a participant who was previously seronegative. For participants who seroconverted during the study but did not report symptoms prior to their seroconversion, the time of SARS-CoV-2 infection was estimated as halfway between the last negative serological test and the subsequent positive serological test, taking into account a 3-week lag for seroconversion among asymptomatic persons [18]. For participants who had symptoms prior to their seroconversion but did not have a positive PCR, it was assumed that the infection occurred on the date of symptom onset.

In addition, the combined effect of prior SARS-CoV-2 infection and COVID-19 vaccination on VE was evaluated, using unvaccinated participants without prior infection as the reference category. For the primary analysis, participants were considered to have had prior SARS-CoV-2 infection if they reported previous PCR-confirmed infection and/or were seropositive for anti-nucleocapsid antibody at enrolment. For the secondary analysis, which included seroconversion as an outcome, participants who received CoronaVac vaccine were excluded, as anti-nucleocapsid antibodies could not be used to distinguish between natural infection and vaccine-induced immunity in these individuals.

Statistical model

VE was estimated as (1 – hazard ratio)*100. Hazard ratios comparing vaccinated and unvaccinated subjects were estimated using Cox proportional hazards models with vaccination as a time-varying exposure (vaccination status of some individuals changed over time from unvaccinated to vaccinated, and from one to two doses); as such, the same participant could contribute person-time to more than one exposure category. Study time was used as the underlying time in the Cox regression.

Unadjusted and adjusted VE estimates were calculated. Both estimates include hospital as a fixed effect. The multi-variable regression model was adjusted using a-priori fixed covariates (hospital, age, sex, prior SARS-CoV-2 infection), and potential confounders (hospital role,

hands-on care, smoking, household size, chronic health condition, body mass index category) that changed the VE estimate by >5% were considered, according to the change-in-estimate approach.

Participants with prior SARS-CoV-2 infection were included in the analysis at the time point they were considered 'at risk' of re-infection, which was defined as 90 days after their most recent positive PCR test or, for participants without a history of a PCR-positive test, 4 weeks after their positive enrolment serology. Participants were considered to be vaccinated with their primary series ≥14 days after their second dose of COVID-19 vaccine.

Person-time contribution was from enrolment, or from the start of time at risk for those with prior SARS-CoV-2 infection, to the earliest of outcome or study exit. Person-time ended on whichever of the following came first: (1) the day of first SARS-CoV-2 infection (symptomatic infection for the primary analysis); (2) the day of receipt of third vaccine dose; or (3) the day of the last weekly questionnaire before loss to follow-up, withdrawal from the study, or censor date for the analysis period (14 December 2021). For the secondary analysis, person-time also ended on the day of the last serological result, or the day of receipt of a dose of CoronaVac. Person-time of persons vaccinated with a single dose was excluded from all analyses from the day they received their first dose, and participants vaccinated with a single dose who had any of the above outcomes were censored from further analysis.

Further analyses and sensitivity analyses

VE analyses were conducted for all vaccines combined, and specifically for the BNT162b2 vaccine. In addition, VE was evaluated during the overall study period and separately for the period in which SARS-CoV-2 B.1.617.2 (Delta variant) was predominant (1 August 2021–14 December 2021), which was defined using sequencing data from study samples along with publicly available data from GISAID [19]. Waning immunity was examined by comparing VE in the period from 14 to 180 days since the second vaccine dose with VE >180 days since the second vaccine dose.

Four sensitivity analyses were also performed: (1) the definition of 'time at risk' was changed from 90 days after infection to 60 days after infection, assuming a shorter duration of protection from infection; (2) 'fully vaccinated' was defined as 7 days after the second dose rather than 14 days after the second dose; (3) participants who were seropositive at enrolment by the WANTAI anti-spike protein assay were included in the 'prior infection' group for the primary analysis; and (4) the start date of the Delta-predominant period was adjusted from 1 August to 1 July 2021.

Results

In total, 1504 participants were enrolled between 19 February and 7 May 2021. Eight participants were excluded (Figure 1). Of the 1496 HCWs included in the analysis, 936 (63%) were from Tirana, 299 (20%) were from Durrës, and 261 (17%) were from Fier. The median age was 44 (IQR 33–53) years, and 1177 (79%) participants were female (Table 1). Only 291 participants (19%) reported any underlying chronic conditions. Most HCWs were nurses or midwives [709 (47%)] or physicians [303 (20%)]. Nearly all participants [1426 (95%)] served in patient-facing roles within the hospital. Age and sex distribution, comorbid conditions and occupation were similar across sites.

At enrolment, 1054 (70%) HCWs had evidence of prior or current SARS-CoV-2 infection through PCR and/or serological assays; 417 (28%) participants reported a PCR-confirmed infection before enrolment, and 18 (1%) had a PCR-positive respiratory sample at enrolment. At enrolment, 981 (66%) participants were positive for SARS-CoV-2 anti-nucleocapsid antibodies. Of the 1097 participants who were seropositive at enrolment by any assay, most [964 (88%)] were positive for both anti-spike antibody and anti-nucleocapsid antibody, indicating prior SARS-CoV-2 infection regardless of vaccination status.

At enrolment, 858 (57%) participants had already received one dose of COVID-19 vaccine (99% ≤5 days prior to enrolment), eight (1%) participants had received two doses, and 630 (42%) participants were unvaccinated. At the end of the analysis period, 1220 (82%) participants had received two doses, 74 (5%) participants had received one dose, and 202 (14%) participants remained unvaccinated. Seventy-one (5%) particpants had received a third dose. Of the 1220 participants who had received two doses by the end of the analysis period, most [1119 (86%)] had received BNT162b2 (Comirnaty, Pfizer), while 162 (13%) had received ChAdOx1 nCoV-19 (Vaxzevria, AstraZeneca), 10 (1%) had received CoronaVac (Sinovac Life Sciences), and three (<1%) reported heterologous vaccination (Table 1). At the end of the analysis period, compared with participants who had received two doses of vaccine, unvaccinated participants were younger [35 years (IQR 29–49) vs 45 years (IQR 35–53)] and more likely to be female [179/202 (89%) vs 938/1220 (77%)], but otherwise demographic, health and occupation characteristics were similar between vaccinated and unvaccinated participants (Table 1).

Seventeen unvaccinated participants developed COVID-19 during the study period (incidence: 24.2 symptomatic infections per 100,000 person-days), and 42 vaccinated participants developed COVID-19 (incidence: 15.8 per 100,000 person-days) (Table 2). Of the 71 cases that occurred during the study period among all participants (including eight cases that occurred in partially vaccinated participants, one case that occurred during the washout period, and three cases that occurred among participants who had received a booster dose), 63 (90%) occurred between 1 August and 14 December 2021, a period during which the Delta variant was predominant (Figure 2). During the study period, 19/28 sequenced SARS-CoV-2 PCR-positive study samples and 24/28 general surveillance SARS-CoV-2 samples from Albania were the Delta variant. The remaining nine samples were the Alpha variant (n=4), Omicron variant (n=2) or Lineage B (n=3).

All 71 participants with COVID-19 completed the 30-day follow-up questionnaire after their positive test. Eighteen participants sought medical care, including four who sought care at the emergency department. None were hospitalized and all reported full recovery at the time of the follow-up survey. The median number of days sick was 4 (IQR 3–7).

Vaccine effectiveness: prevention of symptomatic COVID-19

Adjusted primary series VE against PCR-confirmed symptomatic COVID-19 in the total cohort was 65.1% [95% confidence interval (CI) 37.7–80.5]. Among participants without prior infection, VE was 58.2% (95% CI 15.7–79.3), and among those with prior SARS-CoV-2 infection, VE was 73.6% (95% CI 24.3–90.8) (Table 2). For participants who received the BNT162b2 vaccine, overall VE was 69.5% (95% CI 44.5–83.2). In those without prior infection, BNT162b2 VE was 65.5% (95% CI 29.2–83.2), and in those with prior infection, BNT162b2 VE was 71.3% (95% CI 16.0–90.2).

During the Delta-predominant period, VE of all vaccines combined against COVID-19 in the full cohort was 67.1% (95% CI 38.3–82.5); among those without prior infection, VE in this period was 67.0% (95% CI 27.7–84.9), and among those with prior infection, VE was 68.1% (95% CI 0.9–89.7). Finally, during the Delta-predominant period, BNT162b2-only VE in the full cohort was 68.0% (95% CI 39.7–83.0); among those without prior infection, BNT162b2 VE was 73.0% (95% CI 39.7–87.9), and among those with prior infection, BNT162b2 VE was 65.9% (95% CI -6.0–89.0).

Compared with unvaccinated participants with no evidence of prior SARS-CoV-2 infection, VE against COVID-19 was 62.1% (95% CI 25.3–80.8) for vaccinated participants with no prior infection, and 95.7% (95% CI 89.5–98.3) for vaccinated participants who also had prior infection (hybrid immunity). Protection against COVID-19 re-infection was 84.4% (95% CI 55.5–94.5) for unvaccinated participants who had been infected previously. Findings were similar when the analysis was lim-

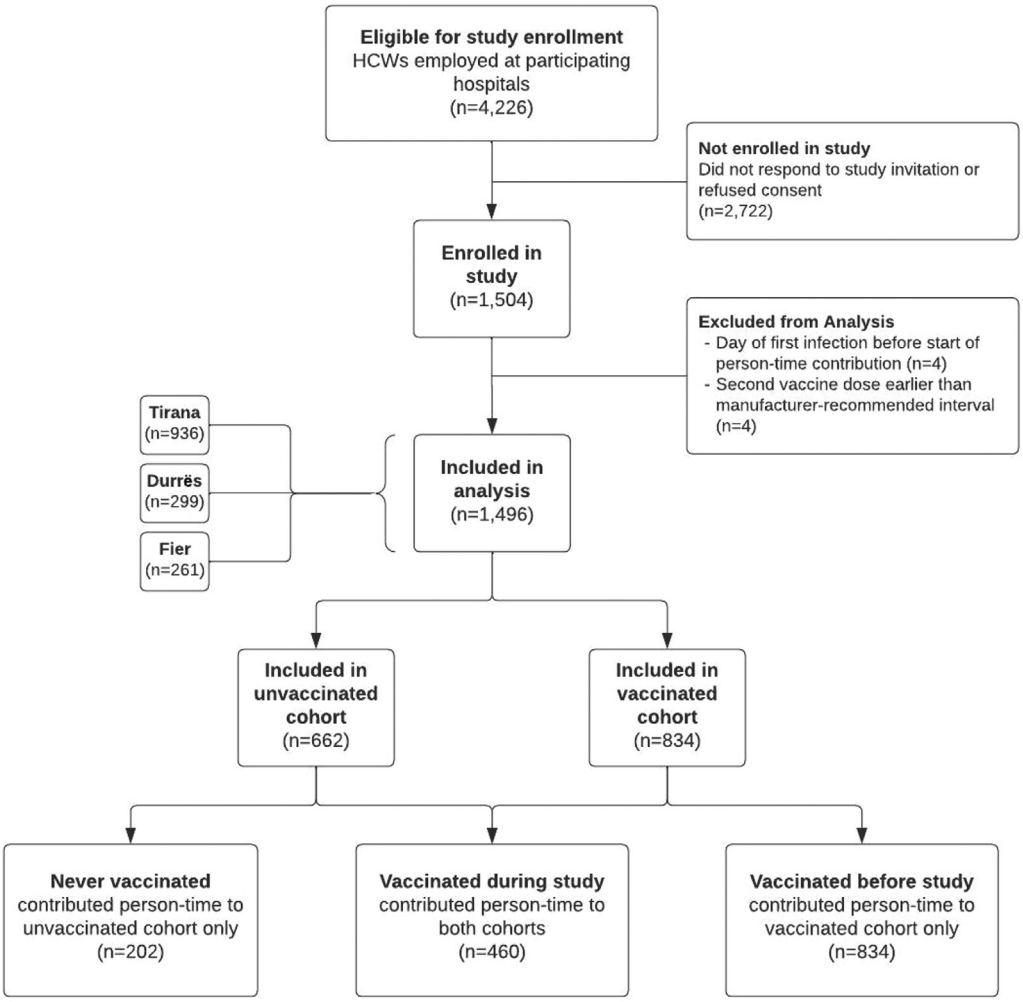

Figure 1. Flowchart illustrating the enrolment of healthcare workers in a coronavirus disease 2019 vaccine effectiveness study, Albania, 2021. HCW, healthcare worker.

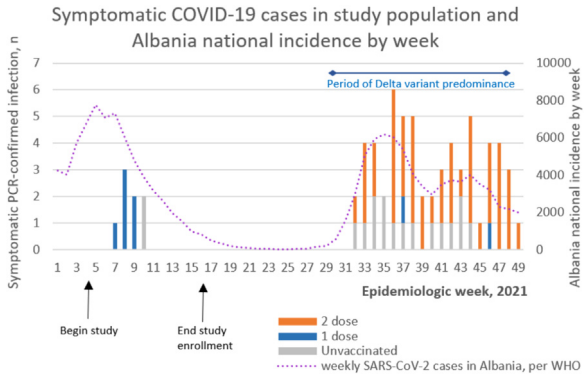

Figure 2. Epicurve showing coronavirus disease 2019 (COVID-19) cases by vaccination status in the study population, and national COVID-19 incidence in Albania, by epidemiologic week, 2021. PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; WHO, World Health Organization.

ited to BNT162b2 alone, the Delta-predominant period alone, and the Delta-predominant period and BNT162b2.

Vaccine effectiveness: prevention of any (asymptomatic or symptomatic) SARS-CoV-2 infection

In the secondary analysis of VE against all SARS-CoV-2 infections, there were 71 SARS-CoV-2 infections (23 PCR-confirmed infections and 48 seroconversions) among unvaccinated participants (122 per 100,000 person-days), and 190 infections (43 PCR-confirmed infections and 147 seroconversions) in vaccinated participants (88 per 100,000 person-days). VE against any infection was 36.9% (95% CI 15.8–52.7) in the full cohort, 53.9% (95% CI 30.4–69.5) among those without prior infection, and 13.7% (95% CI -37.8–46.0) in those with prior infection. For participants who had received BNT162b2 vaccine, VE against infection was 33.3% (95% CI 10.2–50.4) in the full cohort, 53.9% (95% CI 38.0–68.9) in those without prior infection, and 7.9% (95% CI -49.3–43.3) in those with prior infection (Table 3).

Vaccine effectiveness: change in VE by time since vaccination

Sixteen participants who were 14–180 days post-vaccination had COVID-19, of which 11 (69%) cases occurred during the Delta-predominant period; 26 participants who were >180 days post-vaccination had COVID-19, of which 24 (92%) cases occurred during the Delta-predominant period. VE against COVID-19 was 65.7%

Table 1
Participant demographics and clinical characteristics by coronavirus disease 2019 (COVID-19) vaccination status on the last day of follow-up[a] to 14 December 2021

		Total (*n*=1496)	Unvaccinated (*n*=202)	One dose (*n*=74)	Two doses (*n*=1220)
Age (years), median (IQR)					45 (35–53)
Age group (years), *n* (%)	18–29	224 (15)	51 (25)	12 (16)	161 (13)
	30–39	388 (26)	71 (35)	24 (32)	293 (24)
	40–49	368 (25)	31 (15)	18 (24)	319 (26)
	≥50	516 (34)	49 (24)	20 (27)	447 (37)
Sex, *n* (%)	Female	1177 (79)	179 (89)	60 (81)	938 (77)
	Pregnant	32 (3)	28 (16)	1 (2)	3 (<1)
	Breastfeeding	18 (2)	7 (4)	1 (2)	10 (1)
	Male	319 (21)	23 (11)	14 (19)	282 (23)
Hospital, *n* (%)	Tirana	936 (63)	144 (71)	50 (68)	742 (61)
	Durres	299 (20)	22 (11)	5 (7)	272 (22)
	Fier	261 (17)	36 (18)	19 (26)	206 (17)
Chronic conditions, *n* (%)[b]	No	1205 (81)	176 (87)	63 (85)	966 (79)
	Yes	291 (19)	26 (13)	11 (15)	254 (21)
	1	221 (15)	19 (9)	7 (9)	195 (16)
	≥2	70 (5)	7 (3)	4 (5)	59 (5)
Smoker, *n* (%)	Current or previous	273 (18)	17 (8)	19 (26)	237 (19)
	Never	1223 (82)	185 (92)	55 (74)	983 (81)
BMI group, *n* (%)	Underweight or normal	630 (42)	98 (49)	43 (58)	489 (40)
	Overweight	594 (40)	68 (34)	19 (26)	507 (42)
	Obese	272 (18)	36 (18)	12 (16)	224 (18)
Self-assessed health status, *n* (%)	Excellent or very good	1170 (78)	144 (71)	57 (77)	969 (79)
	Good	192 (13)	37 (18)	11 (15)	144 (12)
	Fair or poor	134 (9)	21 (10)	6 (8)	107 (9)
Occupation/role in hospital, *n* (%)	Nurse or midwife	709 (47)	103 (51)	23 (31)	583 (48)
	Physician	303 (20)	21 (10)	21 (28)	261 (21)
	Janitorial staff or food worker	195 (13)	23 (11)	4 (5)	168 (14)
	Other[c]	289 (19)	55 (27)	26 (35)	208 (17)
Patient facing, *n* (%)	Yes	1426 (95)	185 (92)	68 (92)	1173 (96)
	No	70 (5)	17 (8)	6 (8)	47 (4)
Hands-on care, *n* (%)	Yes	901 (60)	115 (57)	38 (51)	748 (61)
	No	595 (40)	87 (43)	36 (49)	472 (39)
Household size, *n* (%)	1–3	575 (38)	85 (42)	25 (34)	465 (38)
	≥4	921 (62)	117 (58)	49 (66)	755 (62)
Brand of vaccine received on the last day of follow-up, *n* (%)	BNT162b2 (Pfizer Comirnaty) alone	1119 (86)	.	43 (58)	1076 (88)
	ChAdOx1 nCoV-19 (Astrazeneca Vaxzevria) alone	162 (13)	.	28 (38)	134 (11)
	Coronavac alone	10 (1)	.	3 (4)	7 (1)
	Heterologous vaccination	3 (<1)	.	0 (0)	3 (0)
Interval between doses for participants who received two doses (days), median (IQR)	BNT162b2 (Pfizer Comirnaty) only	21 (21–21)	.	.	21 (21–21)
	ChAdOx1 nCoV-19 (Astrazeneca Vaxzevria) only	91 (84–98)	.	.	91 (84–98)
	Coronavac only	30 (30–30)			30 (30–30)

IQR, interquartile range; BMI, body mass index.

[a] End of the person-time included in the analysis for each participant. The person-time ended on: (1) the day of the first infection, (2) the day of receipt of a third vaccine dose, (3) the day of receipt of a second vaccine dose if the interval between the first and second doses was shorter than the manufacturer's recommendation, or (4) the day of the last weekly questionnaire before complete loss to follow-up, withdrawal or censor date (14 December 2021).

[b] Include cancer, chronic heart disease, high blood pressure/hypertension, chronic kidney disease, chronic liver disease (such as cirrhosis, hepatitis, fatty liver disease), chronic lung disease (such as asthma, chronic obstructive pulmonary disease), diabetes, immunocompromised (including solid organ transplant and human immunodeficiency virus), neurologic disease (including cerebrovascular disease, epilepsy, multiple sclerosis), obesity, autoimmune disorder.

[c] Includes accountant, administration staff, chemist, courier, driver, economist, general director, lawyer, psychologist, public health specialist, specialist, storekeeper.

(95% CI 26.5–84.0) for participants who were 14–180 days post-vaccination, and 64.6% (95% CI 31.7–81.7) for those who were >180 days post-vaccination. During the Delta-predominant period, VE was 70.2% (95% CI 29.0–87.5) and 66.0% (95% CI 33.0–82.7) for participants who were 14–180 and >180 days post-vaccination, respectively.

Vaccine effectiveness: sensitivity analyses

When the period after infection during which participants were considered not to be at-risk for re-infection was decreased from 90 to 60 days, results were similar to the 90-day analysis. When a participant was considered to be fully vaccinated at 7 days instead of 14 days, VE was also similar. Finally, when the definition of prior infection at enrolment was expanded to include a positive WANTAI anti-spike antibody test for unvaccinated participants and participants who received their first vaccine ≤5 days prior to enrolment, and when the start date of the Delta-predominant period was redefined as 1 July 2021 (instead of 1 August 2021), VE against COVID-19 was largely unchanged.

Discussion

This study of COVID-19 VE among HCWs in Albania, which – to the authors' knowledge – is the first COVID-19 VE study in an upper middle-income country in Europe, found moderate VE against PCR-confirmed COVID-19 among HCWs, most of whom had received two doses of BNT162b2 vaccine, during the Delta-predominant period. In contrast

Table 2
Two-dose vaccine effectiveness (VE) against symptomatic coronavirus disease 2019 (COVID-19), confirmed by polymerase chain reaction, for the full cohort, and stratified by previous severe acute respiratory syndrome coronavirus-2 infection status and for BNT162b2 alone

Two doses (all vaccines)	*n*	Total person-time (days)	Symptomatic COVID-19 infection	Incidence per 100,000 person-days	Unadjusted VE	(95% CI)	Adjusted VE	(95% CI)
Total cohort	1474	.	.	.	.	.	.	.
Unvaccinated		70,367	17	24.2	.	.	.	.
≥14 days from second dose		266,464	42	15.8	62.2	(34.3–78.3)	65.1	(37.7–80.5)
Participants without prior infection	440	.	.	.	.	.	.	.
Unvaccinated		18,829	12	63.7	.	.	.	.
≥14 days from second dose		81,169	34	41.9	60.6	(21.5–80.3)	58.2	(15.7–79.3)
Participants with prior infection	1034	.	.	.	.	.	.	.
Unvaccinated		51,538	5	9.7	.	.	.	.
≥14 days from second dose		185,295	8	4.3	72.9	(23.6–90.4)	73.6	(24.3–90.8)
Two doses (BNT162b2)	*n*	Total person-time (days)	Symptomatic COVID-19 infection	Incidence per 100,000 person-days	Unadjusted VE	(95% CI)	Adjusted VE	(95% CI)
Total cohort	1430	.	.	.	.	.	.	.
Unvaccinated	.	70,367	17	24.2	.	.	.	.
≥14 days from second dose	.	248,388	35	14.1	65.2	(38.3–80.4)	69.5	(44.5–83.2)
Participants without prior infection	440	.	.	.	.	.	.	.
Unvaccinated	.	18,829	12	63.7	.	.	.	.
≥14 days from second dose	.	74,545	28	37.6	63.7	(25.5–82.3)	65.5	(29.2–83.2)
Participants with prior infection	990	.	.	.	.	.	.	.
Unvaccinated	.	51,538	5	9.7	.	.	.	.
≥14 days from second dose	.	173,843	7	4	73.5	(23.4–90.8)	71.3	(16–90.2)

CI, confidence interval.

Table 3
Two-dose vaccine effectiveness (VE) against severe acute respiratory syndrome coronavirus disease-2 (SARS-CoV-2) infection, documented by polymerase chain reaction (PCR) or seroconversion, for the full cohort, and stratified by previous SARS-CoV-2 infection status and for BNT162b2 alone

Two doses (all vaccines)	*n*	Total person-time (days)	PCR-confirmed infection	Seroconversion with Platelia	PCR+ or seroconversion with Platelia	Incidence per 100,000 person-days	Unadjusted VE	(95% CI)	Adjusted VE	(95% CI)
Total cohort	1412									
Unvaccinated		58,260	23	48	71	122				
≥14 days from second dose		214,763	43	147	190	88	39.7	(20.4–54.3)	36.9	(15.8–52.7)
Participants without prior infection	400									
Unvaccinated		13,945	16	30	46	330				
≥14 days from second dose		55,507	34	77	111	200	54.4	(34.9–68)	53.9	(30.4–69.5)
Participants with prior infection	1012									
Unvaccinated		44,315	7	18	25	56				
≥14 days from second dose		159,256	9	70	79	50	16.5	(-31.5–47)	13.7	(-37.8–46)
Two doses (BNT162b2)	***n***	**Total person-time (days)**	**PCR-confirmed infection**	**Seroconversion with Platelia**	**PCR+ or seroconversion with Platelia**	**Incidence per 100,000 person-days**	**Unadjusted VE**	**(95% CI)**	**Adjusted VE**	**(95% CI)**
Total cohort	1373									
Unvaccinated		58,260	23	42	65	112				
≥14 days from second dose		202,724	35	135	170	84	35.2	(13.3–51.5)	33.3	(10.2–50.4)
Participants without prior infection	400									
Unvaccinated		13,945	16	26	42	301				
≥14 days from second dose		51,907	26	70	96	185	51.8	(30–66.8)	53.9	(38–68.9)
Participants with prior infection	973									
Unvaccinated		44,315	7	16	23	52				
≥14 days from second dose		150,817	9	65	74	49	6.8	(-49.3–41.8)	7.9	(-49.3–43.3)

CI, confidence interval.

to previous COVID-19 VE studies conducted among HCWs in HICs that enrolled cohorts with relatively low rates of prior SARS-CoV-2 infection [20–22], HCWs in this study had a high rate of prior infection only 1 year after the start of the pandemic, consistent with trends among HCWs in the Eastern European region, as well as high seroprevalence among the general population in Albania at this time [23]. In this population of previously infected HCWs, VE against COVID-19 was also moderate. This point estimate was higher than the estimated VE among HCWs with no prior infection, which contrasts with other published findings during this timeframe [20,24]. However, this study found very high VE (95.7%) against COVID-19 among HCWs who had been infected previously and later received two doses of COVID-19 vaccine when compared with unvaccinated HCWs without previous infection. These findings of strong protection conferred by hybrid immunity are similar to results of recently published studies in Sweden [25], the UK [9] and Brazil [26]. It is notable that prior SARS-CoV-2 infection reduced the risk of re-infection even in the absence of vaccination, and the present findings of the protective effect of infection alone in the pre-Omicron period have also been demonstrated in other studies [27]. However, infection is not recommended as a strategy to prevent future infections; COVID-19 disease has a number of risks, including severe disease, death and post-infection complications [28].

A contribution of this study is the use of serology in addition to PCR to define prior SARS-CoV-2 infection and to estimate VE against all SARS-CoV-2 infections – both symptomatic and asymptomatic. This combined outcome provided an opportunity to define prior infection comprehensively in the study population. In addition, collecting serological samples quarterly enabled the authors to capture asymptomatic infections or symptomatic infections that were not detected by PCR. In this study, the VE point estimate against PCR-confirmed symptomatic COVID-19 was higher than that for VE against all SARS-CoV-2 infection, defined by the combined outcome, although the 95% CIs overlapped. This trend towards higher COVID-19 VE against symptomatic illness compared with a combined endpoint of symptomatic and asymptomatic infection is consistent with previous findings [29,30]. These results are also consistent with numerous studies showing that COVID-19 vaccines are more effective at preventing severe outcomes, such as hospitalization and death, than they are at preventing milder disease.

While there was a high prevalence (70%) of prior infection in the study population, only 28% were identified by PCR testing prior to enrolment. In addition, 274 (18%) participants seroconverted during the study period without positive PCR tests. These observations suggest that asymptomatic infection may be common, and highlights the importance of robust infection control practices in healthcare settings as part of a larger strategy to reduce nosocomial SARS-CoV-2 transmission from asymptomatic HCWs to staff and patients.

In addition to the use of serology to detect prior infection before enrolment, and to estimate asymptomatic infections during the study period, the strengths of this study include the prospective cohort design and the low number of participants who withdrew or were lost to follow-up. In addition, there was rigorous adherence to the protocol: >95% of participants completed the symptom questionnaire during most weeks; all participants who reported symptoms on their weekly questionnaire had a specimen collected for PCR testing; and serological samples were collected from nearly all participants at enrolment (100%), 3 months (98%) and 6 months (91%). As a result, there were few missing data.

However, this study has some limitations. First, this study measured VE against laboratory-confirmed infection, but was not powered to estimate VE against less common but more severe outcomes, including hospitalization and death. The low number of events also led to notable variability in the results, as reflected in the wide CIs seen for the VE estimates, in particular among participants with prior infection. Additionally, the authors were unable to adjust for timing of prior infections, or variant of prior infection, because the majority of participants had previous infection confirmed only by seropositivity at enrolment, and did not report the date of infection. Finally, the study population may be subject to selection bias – enrolment was voluntary and therefore the HCWs in this study may not fully represent HCWs in Albania or elsewhere (the authors were not able to evaluate representativeness, as demographic information for all eligible HCWs at the study sites was not available). However, two-dose COVID-19 vaccine coverage in this study at the end of the analysis (82%) was similar to two-dose coverage among HCWs in Albania as a whole during the same time period (84%) [31].

In conclusion, this prospective cohort study in an upper-middle income European country found that primary series COVID-19 vaccination was effective in preventing COVID-19 in hospital-based HCWs. The findings support current vaccine policy and highlight the need to continue to promote vaccine uptake, particularly in countries such as Albania, where, as of 19 March 2023, less than half the population has completed a primary vaccine series [8]. In addition, the study findings highlight the added benefit of vaccination in settings with high seroprevalence. Finally, this study is ongoing; future analyses will evaluate VE during the period of Omicron predominance, against future variants of concern, and for additional vaccine doses.

Conflict of interest statement

None declared.

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Disclaimer

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Ethics and study registration

The study protocol was approved by the WHO Ethical Review Committee (Reference Number CERC.0097A) and the Albania Institute of Public Health Ethical Review Committee (Reference Number 156). The CDC Humans Review determined the activity to be a public health evaluation. All participants provided written informed consent. The study is also registered with clinicaltrials.gov (Identifier NCT04811391).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijregi.2023.04.009.

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