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COVID-19 vaccine effectiveness among healthcare workers in Albania (COVE-AL): protocol for a prospective cohort study and cohort baseline data

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ABSTRACT

Introduction Critical questions remain about COVID-19 vaccine effectiveness (VE) in real-world settings, particularly in middle-income countries. We describe a study protocol to evaluate COVID-19 VE in preventing laboratory-confirmed SARS-CoV-2 infection in health workers (HWs) in Albania, an upper-middle-income country.

Methods and analysis In this 12-month prospective cohort study, we enrolled HWs at three hospitals in Albania. HWs are vaccinated through the routine COVID-19 vaccine campaign. Participants completed a baseline survey about demographics, clinical comorbidities, and infection risk behaviours. Baseline serology samples were also collected and tested against the SARS-CoV-2 spike protein, and respiratory swabs were collected and tested for SARS-CoV-2 by RT-PCR. Participants complete weekly symptom questionnaires and symptomatic participants have a respiratory swab collected, which is tested for SARS-CoV-2. At 3, 6, 9 months and 12 months of the study, serology will be collected and tested for antibodies against the SARS-CoV-2 nucleocapsid protein and spike protein. VE will be estimated using a piecewise proportional hazards model (VE=1−HR).

Baseline data From February to May 2021, 1504 HWs were enrolled. The median age was 44 (range: 22–71) and 78% were female. At enrolment, 72% of participants were seropositive for SARS-CoV-2. 56% of participants were vaccinated with one dose, of whom 98% received their first shot within 4 days of enrolment. All HWs received the Pfizer BNT162b2 mRNA COVID-19 vaccine.

Ethics and dissemination The study protocol and procedures were reviewed and approved by the WHO Ethical Review Board, reference number CERC.0097A, and the Albanian Institute of Public Health Ethical Review Board, reference number 156. All participants have provided written informed consent to participate in this study. The primary results of this study will be published in a peer-reviewed journal at the time of completion.

Trial registration number NCT04811391.

Strengths and limitations of this study

► This study is a rigorous, prospective vaccine effectiveness (VE) study using standardised methodology in an upper-middle-income country.

► This study includes serology testing at regular intervals and PCR testing for symptomatic individuals, and therefore, will allow us to identify asymptomatic and symptomatic SARS CoV-2 infections.

► As the SARS-CoV-2 pandemic continues to evolve, and new variants emerge, we will be able to quantify re-infection in previously infected individuals.

► Our study is composed of health workers, who may have different rates of exposure to COVID-19 and different sociodemographic characteristics compared with the general population, which may limit the generalisability of the study to the broader population of Albania.

► Preliminary data indicate high levels of previous infection, which may limit our ability to evaluate VE in a previously uninfected population.

vaccines have reported high efficacy in preventing SARS-CoV-2 infection,[1] there are a number of reasons why COVID-19 vaccine effectiveness (VE) in real-world settings may be different. In real-world settings, factors such as vaccine storage, transport capacity and vaccine administration may vary widely.[2 3] In addition, questions about duration of protection, VE against emerging variants of concern, VE against reinfection and VE among individuals with comorbidities and populations with increased exposure risk, like health workers (HWs), are best answered through studies conducted in real world conditions. To date, a number of early real-world observational studies have demonstrated moderate to high VE in high-income countries against a range of end-points,[4 5] but limited studies to date[6]

INTRODUCTION

COVID-19 vaccination is critical to reducing the impact of the COVID-19 pandemic. While randomised controlled trials of COVID-19

have been published on real-world VE in low-income and middle-income countries (LMICs).

Albania is an upper-middle-income country in Eastern Europe with a population of 2.9 million people.[7] As of 11 January 2022, Albania had reported over 220 000 laboratory-confirmed cases of COVID-19 and over 2,000 COVID-19-related deaths.[8] In December 2020, in accordance with the WHO Strategic Advisory Group of Experts on Immunisation and the European Technical Advisory Group, the Albanian National Immunisation Technical Advisory Group prioritised HWs in Albania as the first target group for COVID-19 vaccine.[9] In December of 2020, about 500 000 doses of the Pfizer BNT162b2 mRNA COVID-19 vaccine were donated by an undisclosed country. The first 11 000 doses arrived in and the first doses of COVID-19 vaccine were administered to health-care workers in Albania.[10]

HWs offer an early opportunity to evaluate COVID-19 VE in a population in which it is critical that an effective vaccine be deployed. HWs are at high risk of acquiring SARS-CoV-2 infection, and have experienced high rates of morbidity and mortality during the COVID-19 pandemic.[9 11] HWs also pose a risk of onward transmission to hospitalised patients, who are often at high risk of serious COVID-19 outcomes.[9]

We describe the protocol and the profile of participants of a study of COVID-19 VE among HWs in Albania, based on a guidance document for VE studies in HWs developed by the WHO Regional Office for Europe.[12] We also describe the characteristics of study participants at enrolment.

METHODS AND ANALYSIS
Objectives
The study is a 12-month prospective longitudinal cohort study, which started in 24 February 2021 and will continue through May 2022. We aim to evaluate COVID-19 VE in preventing SARS-CoV-2 infection in HWs in three hospitals in Albania. The primary objective is to measure COVID-19 VE against any laboratory-confirmed SARS-CoV-2 infection among hospital-based HWs. The secondary objectives include measuring VE against the following outcomes: symptomatic and asymptomatic laboratory-confirmed SARS-CoV-2 infection; reinfection; and infection with new SARS-CoV-2 variants; and estimating VE by age, by various comorbidities, by degree of exposure to COVID-19 patients in the hospital, by physical distancing practices outside of the hospital and by length of time since vaccination.

The primary and secondary objectives of the study and the knowledge gaps they address are outlined in table 1.

Study site and participant selection
This study is being conducted among HWs working in the following three hospitals in Albania: Tirana University Hospital 'Mother Theresa' (3200 HWs), Durres Regional hospital (700 HWs), and Fier Regional Hospital (527 HWs). The three hospitals were chosen for the study because they each employ a large number of HWs, and they are centrally located, facilitating sample transport to the national Institute of Public Health (IPH) laboratories, located in the capital, Tirana.

All HWs at least 18 years old in the three hospitals without contraindications to receive COVID-19 vaccine, which included having had a previous allergic reaction to components of the vaccine, were invited to enrol in the study. We defined HWs as any individual working within the hospital system, including physicians, nurses, respiratory therapists, lab technicians, janitorial staff, food workers and administrative staff, regardless of the extent of direct patient interaction. Preference for recruitment was given to those HWs who received their first dose of the Pfizer BNT162b2 mRNA COVID-19 vaccine no more than 4 days prior to the day of enrolment. Participation was voluntary and did not affect HW's access to receive the COVID-19 vaccine at any time during the study. COVID-19 vaccines are provided to HWs by the hospitals as part of the Albanian vaccine rollout and their access to vaccines is not impacted by the study.

Patient and public involvement
There was no patient involvement in the design of the study.

Recruitment and enrolment
Each participant will be followed for 12 months. After the initial ethical approval, the study was publicised within participating hospitals by word of mouth, flyers and social media. Study staff approached HWs at various highly trafficked points in the hospital, but ensured not to interfere with any routine hospital work.

Study staff described the study in detail, answered all questions, and reviewed the informed consent form with the potential participant in a private area designated for study use. Participation in the study was confidential and was not documented in hospital records. Study participation was not a condition of employment. HWs were invited to participate in the study regardless of their intention to be vaccinated or of their vaccination status. HWs who later choose to get vaccinated will remain in the study; their new vaccination status will be documented and taken into account in the analysis.

Study design
After informed consents were obtained, participants were requested to complete an enrolment questionnaire that included demographic, clinical and epidemiological information, information about vaccination history, occupation-related and community-related behaviour, and recent symptoms. The date of receipt of the first COVID-19 vaccine, for participants who were vaccinated prior to enrolment, was also collected (see online supplemental appendix 1). Participants also provided a blood sample for baseline serological evaluation to assess for previous SARS-CoV-2 infection, and a respiratory sample for COVID-19 Real Time-PCR testing to

Table 1 Knowledge gaps of cohort study to measure COVID-19 vaccine effectiveness among health workers in Albania, and study features intended to address them

Knowledge gap	Study feature
To measure the effectiveness of the COVID-19 vaccine against symptomatic and asymptomatic, laboratory-confirmed SARS CoV-2 infection among health workers	
To date, studies on real-world COVID-19 VE have been conducted in high-income settings. Limited data exists on real-world COVID-19 VE in middle income countries.	This study will be conducted in Albania, an upper middle-income country in Eastern Europe.
The impact of the COVID-19 vaccine on the prevention of asymptomatic disease, an important driver of the COVID-19 pandemic, remains unclear.	Participants with asymptomatic disease will be identified through quarterly serology testing, combined with weekly symptom screening.
VE may vary as new Variants of Concern COVID-19 circulate.	The study will be conducted over the course of a year, so new variants will likely be captured within the circulating population. Additionally, we will perform genetic sequencing on all positive samples to identify the circulating variants over the course of the study.
Does Vaccine effectiveness vary by new strains of SARS-CoV-2?	
The literature is very sparse regarding the effects of previous infection and re-infection with SARS CoV-2 variants.	Sequencing of SARS-CoV-2 positive RT-PCRs will be completed.
To measure COVID-19 Vaccine effectiveness by age	
Limited data exists regarding VE across varying age groups.	A cross-section of hospital workers will be collected and final analysis will be stratified using age.
Duration of COVID-19 vaccine protection against infection	
There is limited data on the duration of VE.	This is a 12-month study that will evaluate VE against PCR-confirmed symptomatic infection and quarterly seroconversion for the duration of the 12 months. Serology samples will be collected at 0, 3, 6, 9, 12 months testing for nucleocapsid protein presence to evaluate for natural infection.
To measure the effectiveness the COVID-19 vaccine in health workers previously infected with COVID-19	
There is limited data on how long previous infection with disease confers protection against reinfection of SARS CoV-2.	We will evaluate the incidence of SARS-CoV-2 re-infection among previously infected healthcare workers comparing vaccinated to unvaccinated individuals.
The utility of COVID-19 vaccine to prevent reinfection in individuals with previous SARS CoV-2 is not well understood.	During the analysis, study participants will be stratified based previous infection prior to vaccination.
VE and duration of VE of one dose of vaccine against infection	
There is sparse data regarding incidence of SARS CoV-2 infection after only one dose of the COVID-19 vaccines.	The study will measure VE, through the use of serology and PCR, in partially and fully vaccinated individuals.
Variation in VE by degree of exposure to COVID-19 patients in the hospital setting and physical distancing practices outside the hospital	
In healthcare workers, a population known to be at high risk for COVID-19, little is known about the impact of activities outside of the workplace is on the incidence of SARS CoV-2 infection.	We will collect information about in-hospital exposure to COVID-19 patients and hospital ward of work for each participant and stratify our analysis accordingly in order to address this question.

VE, vaccine effectiveness.

evaluate for asymptomatic SARS-CoV-2 infection at the time of enrolment. Participants were not blinded to data collectors. However, individuals performing the analysis receive only deidentified information.

For study participants who did not receive their first COVID-19 vaccine at or prior to enrolment but receive their first COVID-19 vaccine 14 days or more after enrolment, an additional blood sample is collected, along with a respiratory sample that will be tested for SARS-CoV-2 by RT-PCR to assess for any asymptomatic infection which may have occurred between enrolment and the time of vaccination. As part of the weekly questionnaire, we ask participants if they received their first or second COVID-19 vaccine in the previous week, and whether they experienced any symptoms in the previous week (see symptom questionnaire (online supplemental appendix 2)). Timing of questionnaires is outlined in table 2.

Table 2 Timing of questionnaires and specimen collection, cohort study to measure COVID-19 vaccine effectiveness among health workers in Albania

Timing in the study	Baseline	Weekly	For symptomatic participants	30 days after a participant tests positive for SARS-CoV-2	Every 3 months
Baseline questionnaire T1	X				
Weekly Symptom questionnaire		X			
Ad hoc symptom questionnaire			X		
30-day follow-up of SARS-CoV-2-positive cases			X	X	
Respiratory sample for PCR testing	X		X		
Serology	X				X

Surveillance

In addition to the weekly questionnaire, oral, nasal or nasopharyngeal PCR specimens are collected from any participant who reports having any of the symptoms, listed in table 3, based on the IPH, Albania case definition for suspected COVID-19 during the weekly questionnaire.[13]

In order to identify test results from SARS-CoV-2 tests performed in locations outside of the study, such as private clinics, study staff cross-reference participants' study ID numbers with the Albanian national SARS-CoV-2 testing database within the web-based information system for infectious disease (ISID), which contains results for all COVID-19 tests performed in the country. For participants who are found to have a SARS-CoV-2 test result outside of the study, an additional symptom questionnaire is administered (online supplemental appendix 3).

Study staff inform HWs about their PCR test results as soon as laboratory testing is complete, whether positive or negative. Staff also provide basic information to COVID-19-positive participants regarding the importance of informing known contacts, when to seek additional medical care, quarantining measures and follow-up with a physician.

In addition, all SARS-CoV-2-positive cases are reported automatically by the IPH laboratory to the relevant hospital infection control team and to the relevant local public health unit via the web-based ISID, as is standard procedure in Albania.

Study staff also contact participants who test positive for SARS-CoV-2 30 days after their positive result in order to administer a brief follow-up questionnaire about their clinical course (online supplemental appendix 4). Participants who test positive for SARS-CoV-2 do not fill out the weekly questionnaire for 90 days following their positive test result. In addition to serology at enrolment, blood samples for serology are collected at 3, 6, 9 and 12 months after enrolment, in order to identify new SARS-CoV-2 infections during the study period.

Study staff

The study team includes staff of the Albanian IPH with experience conducting research, and staff at each of the hospitals. The Albanian IPH provides programmatic and technical support for operations and data management.

Study staff follow infection control guidelines for every interaction with study participants, study team members and laboratory staff. Staff involvement in the study is not related to whether or not they choose to get vaccinated themselves and does not have an impact on their access to receiving the vaccine.

Sample size calculations

The sample size was calculated to allow for robust estimates for the primary study objective, based on estimated vaccination coverage among HWs in Albania, estimated VE, the estimated incidence of SARS-CoV-2 infection over the follow-up time in the unvaccinated study population, and the desired precision.

To meet the desired precision of 5% significance level and a power of 80%, and using the assumptions of a VE

Table 3 Case definition for suspected symptomatic COVID-19 illness, cohort study to measure COVID-19 vaccine effectiveness among health workers in Albania

A participant with any of the following symptoms in the last 7 days is considered a suspected COVID-19 case and will have a respiratory swab collected:

► Fever	► Sore throat	► Diarrhoea
► Cough	► Runny nose	► Altered mental status
► General weakness	► Shortness of breath	► Loss of taste
► Fatigue	► Lack of appetite	► Loss of smell
► Headache	► Nausea	
► Muscle aches	► Vomiting	

of 70% with an incidence of SARS-CoV-2 of 0.05 over the 12-month period and vaccine coverage among participants of 80%, and accounting for a drop-out rate of roughly 10%,we estimated a target population of 1500 HWs.

Data management and ensuring data confidentiality

Data collection and site-level management are conducted using REDCap (Research Electronic Data Capture, Vanderbilt University, Nashville, Tennessee, USA), a secure web application for building and managing online surveys and databases.[14] Within REDCap, a specific project containing all data collection instruments including participant consent forms, enrolment questionnaires, specimen collection, laboratory results, weekly questionnaires and follow-up of symptomatic and COVID-19 positive cases are customised for this study and organised to cover a period of 52 weeks for each participant. Any paper documentation is stored in a secured space and data is uploaded through a secure web connection.

Identifying information is maintained only by the responsible person(s) in each study site in accordance with Ministry of Health and Social Protection requirements. Security measures including password protection and encrypted files are implemented for all study data.

Laboratory procedures
Sample collection

All biological sampling for SARS-CoV-2 RNA is conducted following IPH guidelines on the proper handling and processing of potentially infectious biological materials, based on the latest recommendations from WHO.[15] Dedicated medical staff collect nasal swabs from participants at enrolment and from symptomatic participants during the course of the study. Specimens are transported to the laboratory as soon as possible after collection. If a respiratory specimen is not likely to reach the laboratory and be tested within 96 hours, it is stored, at –70°C, and shipped on ice thermo-boxes. Venipuncture for sera is conducted by hospital-based phlebotomists. Serum specimens are separated from whole blood and stored and shipped at 4°C, or the sera is spun and frozen at - 20°C and shipped directly to the national reference lab at IPH, where they are stored at –20°C or lower until tested.

Testing

All respiratory samples are tested for SARS-CoV-2 by RT-PCR. The RT-PCR testing for SARS-CoV-2 is conducted in the IPH laboratory in Tirana, based on methods implemented and validated in the IPH lab targeting the three major gene targets (N, S and ORF1ab). Testing is conducted with TaqPath COVID-19 CE-IVD kits developed by Thermo Fischer.[16] RT-PCR- positive specimens collected from participants will be further characterised by genetic sequencing at a regional reference laboratory in Europe, following WHO guidelines.[17] in order to understand whether changes in VE could be due in part to virus mutations or specific variant viruses.

Enrolment serology samples were tested using the Wantai antibody ELISA for qualitative detection of total IgG and IgM antibodies to the SARS-Co-V-2 Spike protein.[18] Cut-offs were determined according to manufacturer instructions.[18] Serology samples from enrolment will also be tested for anti-nucleocapsid antibodies. Quarterly serological samples will be tested by anti-nucleocapsid protein antibody tests in order to identify SARS-CoV-2 infection among vaccinated and unvaccinated participants, and by quantitative antispike protein antibody tests in order to identify potential correlates of protection. Additional serological studies may also be performed on a subset of samples.

Analysis plan and statistical considerations
VE analysis

Study participants will be described in terms of total number of eligible HWs, and number and proportion of total who refused participation. Vaccination status will be considered a time-varying exposure (vaccination status of individuals may change over time from unvaccinated to vaccinated; one to two doses). An individual is considered vaccinated with the first dose 14 days after receiving the first vaccine and fully vaccinated 14 days after receiving the second dose of the vaccine. Sensitivity analyses may be performed to evaluate the effectiveness of the vaccine after different intervals following vaccination. If participants receive additional doses of vaccine, these doses will be documented within the study and considered in the analysis.

HRs comparing vaccinated and unvaccinated will be estimated using piecewise exponential survival models. Poisson regression will be used to model these,[19] with the log of person time in the offset, and time split into intervals allowing to estimate baseline hazards of SARS-CoV-2. Individual-level variability will be explored by adding a subject-specific random effect.

VE will be estimated as (1–HR). Follow-up will be from enrolment to the earliest of outcome or study exit. Primary VE analysis will be for the HR for events in the period 14 days from first dose of vaccine onwards, and from the period of 14 days from second dose of vaccine onwards, both compared with events among unvaccinated. Analyses will be carried out in the overall cohort and separately among participants with and without previous infection.

Both unadjusted and adjusted estimates of VE will be presented. We will adjust the multivariable regression model using a priori fixed covariates (hospital, cohort, age, sex and comorbidities) and potential confounders, such as occupation, patient-facing role, performance of aerosol-generating procedures and use of public transport. Bivariable and stratified analyses using participant characteristics will be carried out to better understand potential confounders and effect modifiers. Effect modifiers will be assessed using interaction terms. Factors other than statistical significance (magnitude of measure of effect, biological plausibility) will be used to assess

interactions for relevance. Confounding factors will be assessed by comparing crude and adjusted estimates for each baseline characteristic. We will perform a backward selection procedure to identify other potential confounders. The multivariable regression model will include those variables that change the VE estimates by 5% absolute.

If sample size permits, additional secondary estimates for VE will be calculated by the following parameters:

▶ Partially versus fully vaccinated.
▶ Type of HW and wards.
▶ Age groups.
▶ Sex.
▶ Presence or absence of high-risk conditions for severe illness (see online supplemental appendix 1).[11]
▶ Study week or weeks of the year.
▶ Time since vaccination.
▶ Variants of concern.

Baseline data

The study began recruitment on 19 February 2021, and as of 1 May 2021, 1504 HWs had been enrolled, including 942 (63%) from Tirana University Hospital, 300 (20%) from Durres Hospital and 262 (17%) from Fier Hospital. Participants' demographic information and the results of enrolment serology and PCR testing are described in table 4. Overall, the median age was 44 years (range: 22, 71), 1181 (78%) of participants were female, and 385 (26%) reported having at least one comorbidity. In all, 1434 of 1504 (95%) reported having direct patient contact. 536 (36%) reported having tested positive for COVID-19 prior to enrolment (418 (77%) by PCR, 54 (10%) by serology, 47 (9%) by rapid test and 46 (7%) were unsure of the testing method). At enrolment, 18 (1%) participants were positive for SARS-CoV-2 by RT-PCR and 1085 (72%) participants were positive for SARS-CoV-2 anti-spike protein antibodies based on serology testing. Of the participants who tested positive by RT-PCR at enrolment, 7 out of 18 reported at least one symptom. Overall, 842 (56%) of study participants had received one dose of the Pfizer BNT162b2 mRNA COVID-19 vaccine at enrolment. All vaccinated participants received their first vaccine dose no more than 4 days prior to enrolment. No participant had received two doses of vaccine prior to enrolment, and no participant received a vaccine other than the Pfizer BNT162b2 mRNA COVID-19 vaccine prior to enrolment.

DISCUSSION

In our prospective study of COVID-19 VE in HWs in Albania, we aim to answer critical questions about the real-world effectiveness of COVID-19 vaccines among HWs in an upper-middle-income country. While preliminary reports of real-world VE for mRNA vaccines have shown encouragingly high VE of 86%–90% against SARS CoV-2 infection, these studies were conducted in high-income countries, such as UK, the USA and Israel.[4 5 20]

Table 4 Sociodemographic and clinical characteristics, vaccination status and SARS-CoV-2 serological status of participants at enrolment, cohort study to measure COVID-19 vaccine effectiveness among health workers in Albania

Characteristics	n (%)
Hospital	
Tirana University Hospital	942 (63)
Durres Hospital	300 (20)
Fier Hospital	262 (17)
Gender	
Male	323 (21)
Female	1181 (79)
If female, pregnant	
Yes	32 (2)
No	1149 (77)
If female, breastfeeding	
Yes	18 (1)
No	1163 (77)
Age group	
20–30	269 (18)
31–40	382 (25)
41–50	373 (25)
51–60	424 (28)
Over 60	56 (4)
Pre-existing medical conditions	
High blood pressure/hypertension	121 (8)
Obesity	80 (5)
Diabetes	41 (3)
Chronic lung disease (such as asthma, Chronic Obstructive Pulmonary Disease (COPD), bronchitis)	31(2)
Chronic heart disease, excluding high blood pressure	29 (2)
Autoimmune disorder	29 (2)
Cancer	21 (1)
Neurological disease: including cerebrovascular disease, epilepsy and multiple sclerosis	13 (0.8)
Chronic liver disease (such as cirrhosis, hepatitis, fatty liver disease)	12 (0.8)
Chronic kidney disease	7 (0.5)
Immunocompromised, including solid organ transplant and HIV	1 (0.06)
Smoking	
Current or previous smoker	273 (14)
Never smoked	1231 (86)
Occupation	
Nurse	691 (46)

Continued

Table 4 Continued	
Characteristics	**n (%)**
Medical doctor	305 (20)
Midwife	30 (2)
Laboratory technician	42 (3)
Biologist	0 (0)
Pharmacist	8 (0.5)
Janitorial staff	190 (13)
Food worker	5 (0.3)
Social worker	6 (0.3)
Radiology technician	22 (1)
Other*	214 (14)
Clinical health worker (hands on medical care)	
Yes	908 (60)
No	596 (40)
Received a positive laboratory test for SARS CoV-2 since January 2020	
Yes	536 (36)
No	968 (64)
If yes	
PCR	418 (28)
Rapid test	47 (9)
Serology	54 (10)
Don't know	36 (7)
Received at least 1 dose of the COVID-19 vaccine	
Yes	842 (56)
No	662 (44)
Brand of vaccine if yes	
Pfizer	842 (56)
Enrolment PCR results	
Positive	18 (1)
Negative	1486 (99)
Enrolment serology results	
Positive	1085 (72)
Negative	414 (28)
iIndeterminant (borderline)	5 (0.3)

*Other includes: accountant (10), administrative staff (55), archivist (1), scientist (4), couriers (5), drivers (20), economists (27), Information Technologists (2), Lawyer (5), specialists (29), police officer (5), psychologists (6), physiotherapists (5).

Effectiveness may vary in lower-resource settings, in part due to challenges such as vaccine transport, storage, administration and associated technical skill.[3] LMICs could also face varying levels of virus transmission, in part due to lower vaccine coverage and different circulating viruses. As of 11 January, over 460 000 people (41% of the population) in Albania had received at least one dose of COVID-19 vaccine,[21] much lower than the one-dose coverage rates in the UK (76%), the USA (73%) and Israel (72%) by the same date.[21] Understanding VE in a middle-income country such as Albania provides important information regarding allocation and effective vaccine distribution in similar contexts. Data from VE studies can impact local funding of vaccines and help build trust in local vaccine roll-outs.[22]

Our protocol was adapted from the WHO/Europe guidance document for cohort studies to measure COVID-19 VE in HWs.[12] Similar studies based on the same guidance document are being conducted in other countries within the Eastern European region, and will provide an opportunity to compare country-level VE and to estimate VE using aggregated data. Similar studies evaluating VE in HWs have been conducted in the US by the HEROES/RECOVER network as well.[20]

The enrolment profile of participants in our study offers unique challenges and opportunities. Over 70% of our study participants were seropositive for SARS-CoV-2 anti-spike antibodies on enrolment, a figure that is higher than the 48% seropositivity reported from a seroprevalence survey of the general population of Tirana, Albania during December 2020,[23] which was nearly 2 months prior to the start of our study. Nearly all (98%) vaccinated participants had serology drawn within 4 days of their first vaccination, making it very unlikely that this seropositivity reflects a vaccine-induced antibody response. While false positives are a consideration from the Wantai SARS-CoV-2 Ab Elisa due to cross-reactivity from pre-existing antibodies, the test has a been found to have sensitivity of 99%.[24]

While previously infected study participants are likely to be at reduced risk for reinfection for at least 5–6 months,[25] the study population represents real-world conditions, and future recommendations about vaccine use will need to made taking into account the fact that many populations have high seroprevalence. We will test quarterly serologies using an antinucleocapsid antibody test, which will allow us to measure natural infection among both vaccinated and unvaccinated participants. Because this is a 15-month study, we hope to be able to draw conclusions about duration of VE, duration of natural immunity, with or without vaccine, and VE against Variants of Concern that may appear and could escape existing vaccines and/or natural immunity, as has recently been demonstrated with the delta and omicron variants.[26–28]

A strength of our study is the novelty of conducting a rigorous, prospective VE study using standardised methodology in an upper-middle-income country.[12] Another strength is the use of a very sensitive definition for suspected symptomatic cases of COVID-19, which will ensure that even mildly symptomatic cases will be captured in our analysis. Additionally, testing serology samples using anti-nucleocapsid antibody testing will allow us to identify asymptomatic infections or symptomatic infections not captured by PCR screening and distinguish vaccine-induced immune response from

infection-induced immunity. By capturing serology and nasal swabs at enrolment, prior infection will be incorporated into our analysis. In addition, the use of the COVID-19 Albanian National Database will allow for close monitoring of COVID-19 tests, include those performed by study participants outside of the study.

Our study has a number of limitations. Our study is subject to selection bias; the study was voluntary and although we tried to recruit HWs broadly in the three hospitals, it is possible that the HWs in our study are not representative of all HWs in the three hospitals or of the general population in Albania.

In addition, our study includes HWs, who are likely to have different rates of exposure to COVID-19 and different sociodemographic characteristics compared with the general population. As a result, our study results may not be generalisable to the broader population of Albania. Because of the high levels of previous infection, we may not be adequately powered to show VE in a previously uninfected population. However, the added value of vaccine in preventing reinfection in previously infected individuals is an important gap in global evidence; our study may allow us to answer this question. Additionally, the SARS-CoV-2 pandemic continues to evolve, resulting in multiple variants of concern, such as the delta and omicron variants, which have been associated with vaccine breakthrough infections, and meaningfully reduced VE for mild and, to a lesser extent, severe illness.[28] It is unclear to what extent natural infection will protect from future VoCs, even with the addition of partial or full vaccination, but a similar pattern may emerge. Furthermore, given the potentially low number of cases among previously infected individuals,[25] we may be inadequately powered to evaluate secondary VE objectives such as VE by age and comorbidity or by variant infection.

Understanding the VE of the COVID-19 vaccine in HWs in Albania will provide critical information about the performance of COVID-19 vaccines in an upper-middle-income country over the course a 12-month period. Our findings should inform decisions about vaccine use in Albania and could be helpful for other countries in the region and around the world, which will likely be facing very similar questions about vaccine policy.

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