BMJ Open

Cohort Study to Measure COVID-19 Vaccine Effectiveness among Health Workers in Albania (COVE-AL): Study Protocol and Description of Participants at Enrollment

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-057741
Article Type:	Protocol
Date Submitted by the Author:	28-Sep-2021
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Keywords:	COVID-19, Infection control < INFECTIOUS DISEASES, Public health < INFECTIOUS DISEASES, Health & safety < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

Title: Cohort Study to Measure COVID-19 Vaccine Effectiveness among Health Workers in Albania (COVE-AL): Study Protocol and Description of Participants at Enrollment

Current Manuscript Word Count (not including title, references, tables/figures): 3834

Abstract word count: 300

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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 3 hospitals in Albania. HWs were vaccinated through the routine COVID-19 vaccine campaign. Participants completed a baseline survey about

demographics, clinical comorbidities, and infection risk behaviors. Serology samples were 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 are complete weekly symptom questionnaires. Symptomatic participants have a respiratory swab collected, and 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 piece-wise proportional hazards model (VE = 1 - hazard ratio [HR]).

Results:

From February, 2021- May, 2021, 1504 HWs were enrolled. The median age was 44 (range: 22-71) and 78% were female. At enrollment, 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 enrollment. All HWs received the Pfizer BNT162b2 mRNA COVID-19 vaccine.

Discussion:

Our prospective VE study among HWs will provide critical data about real-world COVID-19 VE, including duration of vaccine and naturally derived protection.

Ethics and dissemination:

The study protocol and procedures were reviewed and approved by the WHO and Albanian Institute of Public Health (IPH) Ethical Review Boards. Funding is provided by the WHO Regional office For Europe and the United States Centers for Disease Control and Prevention (US CDC).

Registration:

This study has been registered with clinicaltrials.gov (Identifier NCT04811391).

Strengths and Limitations of this Study

- This study is a rigorous, prospective vaccine effectiveness study using standardized methodology in an upper middle-income country.
- A very sensitive definition, and PCR and serology testing at regular intervals will allow us to identify asymptomatic and symptomatic infections.
- As the SARS-CoV-2 pandemic continues to evolve, resulting in multiple variants, we will be able to quantify re-infection in previously individuals.
- Our study is composed of health workers, who may have different rates of exposure to COVID-19 and different sociodemographic characteristics compared to the general population, which may limit the generalizability of the study to the broader population of Albania.
- Preliminary results indicate high levels of previous infection, and which may limit our ability to evaluate VE in a previously uninfected population.

Introduction:

COVID-19 vaccination is critical to reducing the impact of the COVID-19 pandemic. While randomized controlled trials (RCTs) of COVID-19 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, 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] have been published on real-world VE in low- 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 June 1, 2021, Albania had reported over 132,000 laboratory-confirmed cases of COVID-19 and over 2,000 COVID-19-related deaths,[8] out of a population of 2.8 million.[9] In December 2020, in accordance with the WHO Strategic Advisory Group of Experts on Immunization (SAGE) and the European Technical Advisory Group, the Albanian National Immunization Technical Advisory Group prioritized health workers (HWs) in Albania as the first target group for COVID-19 vaccine.[10] In December of 2020, about 500,000 doses of the Pfizer BNT162b2 mRNA COVID-19 vaccine were donated by an undisclosed country with the first 11,000 doses arriving in January 2021.[11] On January 12, 2021, the first doses of COVID-19 vaccine were administered to healthcare workers in Albania.[11,12]

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 during the COVID-19 pandemic.[14] HWs also pose a risk of onward transmission to hospitalized patients, who are often at high risk of serious COVID-19 outcomes.[15]

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.[13] We also describe the characteristics of study participants at enrollment.

Methods and analysis

Objectives

The study is a 12-month prospective longitudinal cohort study, which started in February 2021 and will continue through March 2022, 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 health workers. 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 are large, each employing a large number of health workers, and 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 who do not have contraindications to receive COVID-19 vaccine, specifically previous allergic reactions to components of the vaccine were invited to enroll in the study. HWs include 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 enrollment. Participation is voluntary and does not affect HW's access to receive the COVID-19 vaccine at any time during the study. Vaccinations were provided by the hospitals as part of the Albanian vaccine rollout and were not impacted by the study.

Patient and Public Involvement:

There was no patient involvement in the design of the study.

Recruitment and Enrollment

Each participant will be followed for 12 months. After approval, the study was publicized 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 is confidential and anonymous from the hospital records, and study participation is 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. Health workers 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 enrollment questionnaire that included demographic, clinical, and epidemiological information, information about vaccination history, occupation- and community-related behavior, and recent symptoms. The date of the first Covid vaccine shot for those who chose to be vaccinated was collected as well (see Appendix 1); to provide a blood sample for baseline serological evaluation to assess for previous SARS-CoV-2 infection; and to provide a respiratory sample for COVID-19 RT-PCR testing to evaluate for asymptomatic SARS-CoV-2 infection at the time of enrollment.

For study participants who do not receive their first COVID-19 vaccine at enrollment but receive their first COVID-19 vaccine 14 days or more after enrollment, 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 asymptomatic infection

which may have occurred between enrollment 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. In addition, a brief questionnaire about recent symptoms is administered. Timing of questionnaires is outlined in Table 2.

Surveillance:

Following enrollment, for the duration of the study, every week participants will be asked to complete a short questionnaire by phone, email, paper or online about whether or not they had symptoms consistent with COVID-19 and whether they have received a COVID-19 vaccine in the past week (see symptom questionnaire) (Appendix 2).

Oral, nasal or nasopharyngeal PCR specimens will be collected from any participant who reports having any of the symptoms, listed in Table 3 based on the Institute of Public Health, Albania case definition for suspected COVID-19 during the weekly questionnaire.[16]

In order to identify test results from SARS-CoV-2 tests performed in locations outside of the study, such as private clinics, study staff will 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 will be administered (Appendix 3).

Study staff will inform HWs about their PCR test results as soon as laboratory testing is complete, whether positive or negative. Staff will 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 will be 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 information system for infectious diseases, as is standard procedure in Albania.

Study staff will 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 (Appendix 4). Participants who test positive for SARS-CoV-2 will not need to fill out the weekly questionnaire for 90 days following their positive test result. In addition to serology at enrollment, blood samples for serology will be collected at 3, 6, 9 months, and 12 months, in order to identify asymptomatic cases during the study period.

Study Staff

The study team includes staff of the Albanian Institute of Public Health (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 will 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 will not have an impact on their access to receiving vaccine.

Sample Size Calculations

Sample size was calculated to allow for robust estimates for the primary study objective, based on estimated vaccination coverage among health workers 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 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%[13],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, TN, USA) , a secure web application for building and managing online surveys and databases.[17] Within REDCap, a specific project containing all data collection instruments including participant consent forms, enrollment questionnaires, specimen collection, laboratory results, weekly questionnaires and follow up of symptomatic and COVID-19 positive cases will be customized for this study and organized to cover a period of 52 weeks for each participant. Any paper documentation will be stored in a secured space and data is uploaded through a secure web connection.

Identifying information will be 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 will be implemented for all study data.

Laboratory Procedures:

Sample Collection

All biological sampling for SARS-CoV-2 RNA will be conducted following IPH guidelines on the proper handling and processing of potentially infectious biological materials, based on the latest recommendations

from WHO[18]. Dedicated medical staff will collect nasal from participants at enrollment and from symptomatic participants during the course of the study. Specimens will be 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 will be stored, at –70 °C, and shipped on ice thermo-boxes. Venipuncture for sera will be collected by hospital-based phlebotomists. Serum specimens will be separated from whole blood and stored and shipped at 4 °C or sera spun and frozen to - 20°C and shipped directly to the national reference lab at IPH, where they should be stored at -20°C or lower until tested.

Testing

All respiratory samples will be tested for SARS-CoV-2 by RT-PCR. The Real-Time PCR testing for SARS-CoV-2 will be 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 will be conducted with TaqPath COVID-19 CE-IVD kits developed by Thermo Fischer.[19] RT-PCR- positive specimens collected from participants will be further characterized by genetic sequencing at a regional reference laboratory in Europe, following WHO guidelines,[20] in order to understand whether changes in VE could be due in part to virus mutations or specific variant viruses.

Enrollment 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.[21] Cut-offs were determined according to manufacturer instructions.[21] Serology samples from enrollment will also be tested for anti-nucleocapsid antibodies. Quarterly serological samples will be tested by anti-nucleocapsid protein antibody tests in order to identify natural infection among vaccinated and unvaccinated participants, and by quantitative anti-spike 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

Vaccine effectiveness 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 will be 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.

Hazard ratios comparing vaccinated and unvaccinated will be estimated using piece-wise exponential survival models. Poisson regression will be used to model these,[22] 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 – hazard ratio [HR]). Follow-up will be from enrollment to the earliest of outcome or study exit. Primary VE analysis will be for the hazard ratio 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 to events among unvaccinated. Analyses will be carried out in the overall cohort and separately among participants with and without previous infection, if sample size allows.

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 vs. fully vaccinated;
- type of HW and wards;
- age groups;
- sex;
- presence or absence of high-risk conditions for severe illness (see appendix 1)[13];
- study week or weeks of the year;
- time since vaccination
- variants of concern

Profile of study population:

The study began recruitment on Feb 19, 2021, and as of May 1, 2021, 1504 HWs had been enrolled, including 942 (63%) from Tirana University Hospital, 300 (20%) from Durres Hospital and 262 (17%) from Fier Hospital. Demographic information and the results of enrollment 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 co-morbidity. In all, 1434 of 1504 (95%)] reported having direct patient contact. 536 (36%) reported having tested positive for COVID-19 prior to enrollment (418 (77%) by PCR, 54 (10%) by serology, 47 (9%) by rapid test and 46 (7%) were unsure of the testing method). At enrollment, 18 (1%) of participants were positive for SARS-CoV-2 by RT-PCR and 1085 (72%) of participants were positive for SARS-CoV-2 anti-spike protein antibodies based on serology

testing. Of the participants who tested positive by RT-PCR, 7 out of 18 reported at least 1 symptom. Overall, 842 (56%) of study participants had received one dose of the Pfizer BNT162b2 mRNA COVID-19 vaccine vaccine at enrollment. All vaccinated participants received. their first vaccine dose no more than 4 days prior to enrollment. No participants had received two doses of vaccine prior to enrollment, and no participants received a vaccine other than the Pfizer BNT162b2 mRNA COVID-19 vaccine prior to enrollment.

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 US and Israel.[4,5,23] Effectiveness may vary in lower-resource settings, in part due to challenges such as vaccine transport, storage, administration and associated technical skill.[3] Low- and middle-income countries could also face varying levels of virus transmission, in part due to lower vaccine coverage, and different circulating viruses. As of June 1, over 460,000 people (17% of the population) in Albania had received at least one dose of COVID-19 vaccine,[24] much lower than the one-dose coverage rates in the United Kingdom (58%), the United States of America (50%) and Israel (63%) by the same date.[4] Understanding VE in a middle-income country such as Albania provides important information regarding allocation and effective vaccine distribution in similar contexts. This understanding has a critical impact on local funding of vaccines as well as building trust in local vaccine rollouts.[25]

Our protocol was adapted from the WHO/Europe guidance document for cohort studies to measure COVID-19 VE in HWs[13]. 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.[26]

The enrollment 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 enrollment, a figure that is higher than the 48% seropositivity reported from a seroprevalence survey of the general population of Tirana, Albania during December 2020.[27] which was nearly 2 months prior to the start of our study. Nearly all (98%) of vaccinated participants had serology drawn within 4 days of their first vaccination, making it very unlikely that 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%.[28]

While previously infected study participants are likely to be at reduced risk for reinfection for at least 5-6 months,[29] 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 anti-nucleocapsid antibody test, which will allow us to measure natural infection among both vaccinated and unvaccinated participants. Because this is a 12-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 variant for partially vaccinated individuals.[30]

A strength of our study is the novelty of conducting a rigorous, prospective VE study using standardized methodology in an upper middle-income country.[13] 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 enrollment, prior infection will be incorporated into our analysis. In addition, the use of the 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 to the general population. As a result, study results are not be generalizable 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 re-infection 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 variant, which have been associated with vaccine breakthrough infections, and meaningfully reduced vaccine effectiveness for mild and, to a lesser extent severe, illness.[31] 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,[29]we may be inadequately powered to evaluate secondary VE objectives such as VE by age and co-morbidity 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.

Ethics/Dissemination:

The study protocol and procedures were reviewed and approved by the WHO Ethical Review Board as well as the IPH institutional review board. All data is stored in REDCap and uploaded to the Epifiles database. Stakeholders have user-specific defined access.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

This study has been registered with clinicaltrials.gov (Identifier NCT04811391). A manuscript with the results of the primary study will be published in a peer-reviewed journal.

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Contributorship statement:

All authors made substantial contributions to the conception or design of the work, as well as the acquisition, analysis and interpretation of data for the work. All authors were involved in drafting and revising the document for intellectual content and provided final approval of the version to be published.

All authors are in agreement to be accountable for all aspects of this work in regards to accuracy and integrity.

Competing Interests: There are no competing interests to report.

Funding:

The study is funded by the WHO Regional Office for Europe the United States Centers for Disease Control and prevention (US CDC) and conducted by the Institute of Public Health (IPH) in Albania. There is no associated award/grant number associated.

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Tables and Figures

Table 1. Knowledge gaps of Cohort Study to Measure COVID-19 Vaccine Effectiveness among Health Workers in Albania (COVE-AL), 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 re-infection of SARS CoV-2	We will evaluate the incidence of SARS-CoV-2 re-infection among previously infected health care workers comparing vaccinated to unvaccinated individuals.
The utility of COVID-19 vaccine to prevent re-infection 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.

Table 2: Timing of questionnaires and specimen collection, Cohort Study to Measure COVID-19 Vaccine Effectiveness among Health Workers in Albania (COVE-AL)

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

Table 3: Case Definition for Suspected symptomatic Covid-19 illness, Cohort Study to Measure COVID-19 Vaccine Effectiveness among Health Workers in Albania (COVE-AL).

- 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	• Diarrhea
• 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	

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)

Table 4: Sociodemographic and clinical Characteristics, vaccination status, and SARS-CoV-2 serological status of Participants at Enrollment, Cohort Study to Measure COVID-19 Vaccine Effectiveness among Health Workers in Albania (COVE-AL).

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, 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)
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)
Enrollment PCR Results	
Positive	18 (1)
Negative	1486 (99)
Enrollment Serology Results	
Positive	1085 (72)
Negative	414 (28)
Cut-off (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)

Enrollment Questionnaire

INSTRUCTIONS:
This survey will take about 5-10 minutes to complete. If you have any questions, please contact [XXXXX] at [-XXXXXXXX] or email XXXXXX.
Thank you again for your time.

A. Demographics, SARS-CoV-2 history and vaccination history

A1. What is your age?

A2. Are you male or female?

A2a. If you are female:

Are you pregnant?: (If yes, specify trimester)

Are you Breastfeeding?:

A3. What is your height in cm?

A4. What is your weight in kg?

A5. Have you ever been diagnosed with any of the following?

- ☐ Cancer
- ☐ Chronic Heart Disease, excluding high blood pressure
- ☐ High blood pressure/Hypertension
- ☐ Chronic Kidney Disease
- ☐ Chronic Liver Disease (such as cirrhosis, hepatitis, fatty liver disease)
- ☐ Chronic Lung Disease (such as asthma, COPD, bronchitis, etc…)
- ☐ Diabetes
- ☐ Immunocompromised, including solid organ transplant and HIV
- ☐ Neurological Disease, including cerebrovascular disease, epilepsy, multiple sclerosis, etc…
- ☐ Obesity
- ☐ Autoimmune disorder

A6. Do you currently smoke?

- ☐ Yes
- ☐ No

A6a: If no, have you smoked previously?

- ☐ Yes
- ☐ No

A7. How many people (not including yourself) do you live with?

- ☐ 0
- ☐ 1
- ☐ 2
- ☐ 3
- ☐ 4
- ☐ 5
- ☐ 6 or more

A8. Since January 2020, have you ever received a positive laboratory test for SARS-CoV-2, the virus that causes COVID-19?

- ☐ Yes
- ☐ No

A8a. If yes, when was the positive test (date), and what kind of test was performed (PCR or rapid test or serology)

- ☐ PCR (nasal swab)
- ☐ Rapid Test (nasal swab)
- ☐ Serology Test (a blood test)
- ☐ Don't remember

Date of Test _____

(Allow option for multiple positive test results)

COVID 19 Vaccination Questions

A9. When the COVID -19 vaccine becomes available, what are the chances that you will choose to receive a COVID-19 vaccination if you are offered one?

- ☐ Almost Zero Chance
- ☐ Very Small Chance
- ☐ Small
- ☐ Moderate
- ☐ Large
- ☐ Very Large Chance

☐ Almost Certain
☐ I have already received a COVID-19 vaccine: Date: _____

Vaccination history **COVID vaccine**	
1. Do you have a contraindication for the COVID-19 vaccine?	☐ Yes ☐ No ☐ Unknown
2. Have you received the first dose of any COVID-19 vaccine?	☐ Yes ☐ No ☐ Unknown
3. If yes, what was the date of the first dose? (dd/mm/yyyy)	___/___/___
4. Which vaccine did you receive? (product name)	
5. Mode of vaccine ascertainment (to be the verified by study staff)	☐ = vaccination card ☐ = vaccination registry ☐ = self-report ☐ = other (specify_____) ☐ = not documented
6. What was the Batch of the vaccine received?	Please provide the match number from the above documents or state ☐ Unknown
7. Have you received a second dose of the COVID-19 vaccine?	☐ Yes ☐ No ☐ Unknown
8. If yes, what day did you receive the second dose (dd/mm/yyyy)	___/___/___
9. Which kind of vaccine did you receive for the second dose (product name)	
10. What was the Batch number of the second dose vaccine you received?	Please provide the match number from the ascertainment documents or state ☐ Unknown
11. Mode of vaccine ascertainment of the second dose (to be verified by study staff)	☐ = vaccination card ☐ = vaccination registry ☐ = self-report ☐ = other (specify_____)

	☐ = not documented

Did you receive the influenza vaccine in the past winter (since September 2020)?

☐ Yes
☐ No

B. Occupation and Work Responsibilities

B1. In what departments, wards, or parts of your health facility do you regularly work? Check all that apply.

☐ Hospital
☐ Emergency Department
☐ Critical Care or Intensive Care Unit
☐ Infectious Diseases
☐ Lung diseases
☐ Internal Medicine and/or Medical Specialties
☐ Pediatrics and/or Pediatric Specialties
☐ Surgery and/or Surgical Specialties
☐ Gynecology and/or Obstetrics
☐ Oncology and/or Hematology
☐ Dentistry
☐ Radiology
☐ Outpatient clinic
☐ Pharmacy
☐ Laboratory
☐ Nutrition
☐ Social Assistance
☐ Physiotherapy
☐ Occupational therapy
☐ *Other*

B1a:_Other department or ward, please SPECIFY: _____

B2. What is your current job/occupation at the hospital?

☐ Nurse
☐ Medical doctor
☐ Midwife

- ☐ Laboratory technician
- ☐ Biologist
- ☐ Pharmacist
- ☐ Janitorial staff
- ☐ Food worker
- ☐ Social Worker
- ☐ Radiology Technician
- ☐ *Other*

B3. With which groups of patients do you have regular or daily face-to-face contact? Check all that apply.

- ☐ Infants aged <1 year
- ☐ Children aged 1-12 years
- ☐ Teenagers aged 13-19
- ☐ Adults aged 20-64
- ☐ Older adults aged 65 and older
- ☐ Pregnant women

B4. Are you a clinical health worker (such as a doctor, nurse, or medical technician) who provides hands-on medical care to patients?

- ☐ Yes
- ☐ No

B4a. [If B4= "Yes"] Do you perform any of the following procedures regularly (on most workdays)? This means you do this task yourself (and not simply oversee). Check any or all that apply.

- ☐ Collect a respiratory specimen using a swab
- ☐ Collect a sputum specimen
- ☐ Administer medication using a nebulizer
- ☐ Apply nasal cannula (two pronged tube for nasal oxygen)
- ☐ Apply oxygen face mask
- ☐ Perform tracheal intubation
- ☐ Insert a nasogastric (feeding) tube
- ☐ Perform manual ventilation
- ☐ Apply mechanical ventilation

- ☐ Perform suction of fluids or secretions
- ☐ Perform chest physiotherapy (such as chest percussion)
- ☐ Perform bedside bronchoscopy

C. Health Status

C1. How would you describe your current health overall?

- ☐ Excellent
- ☐ Very Good
- ☐ Good
- ☐ Fair
- ☐ Poor

E. Questions about Illness, Vaccines, and Missing Work

E1. How much do you know about the Covid-19 vaccine?

- ☐ Nothing at all
- ☐ A little
- ☐ Some
- ☐ A lot
- ☐ A great deal

E2. COVID-19 vaccination is safe.

- ☐ Strongly agree
- ☐ Mildly agree
- ☐ Neutral
- ☐ Mildly disagree
- ☐ Strongly disagree

E3. If you are unable to or don't get a COVID-19 vaccination, what do you think your chance of getting the COVID-19 will be?

- ☐ Almost Zero Chance
- ☐ Very Small Chance
- ☐ Small
- ☐ Moderate
- ☐ Large
- ☐ Very Large Chance

E4. How effective do you think the COVID-19 vaccine is in preventing you from getting sick with COVID-19?

- ☐ Extremely effective
- ☐ Very effective
- ☐ Somewhat effective
- ☐ Not too effective
- ☐ Not at all effective

E5. If you get a COVID-19 vaccination, what do you think your chance of getting sick with COVID-19 will be this year…?

- ☐ Almost Zero Chance
- ☐ Very Small Chance
- ☐ Small Chance
- ☐ Moderate Chance
- ☐ Large Chance
- ☐ Very Large Chance

E6. If I get an COVID-19 vaccination, I will be less likely to miss work because of getting sick with COVID-19.

- ☐ Strongly agree
- ☐ Mildly agree
- ☐ Neutral
- ☐ Mildly disagree
- ☐ Strongly disagree

E7. Compared to your co-workers at your health facility, how favorable or unfavorable is your attitude toward COVID-19 vaccination?

- ☐ Extremely more favorable
- ☐ Much more favorable
- ☐ Slightly more favorable
- ☐ Average for co-workers at my facility
- ☐ Slightly less favorable
- ☐ Much less favorable
- ☐ Extremely less favorable

E8. If I don't get a COVID-19 vaccination, I will regret it.

- ☐ Strongly agree

☐ Mildly agree
☐ Neutral
☐ Mildly disagree
☐ Strongly disagree

E9. How worried are you about getting sick with COVID-19 during the next 12 months?

☐ Extremely worried
☐ Very worried
☐ Moderately worried
☐ A little worried
☐ Not at all worried

E10. I get sick with influenza and other respiratory viruses more easily than other people my age.

☐ Strongly agree
☐ Mildly agree
☐ Neutral
☐ Mildly disagree
☐ Strongly disagree

E11. Employees at my healthcare facility are encouraged to go home if they have respiratory symptoms at work.

☐ Strongly agree
☐ Mildly agree
☐ Neutral
☐ Mildly disagree
☐ Strongly disagree

F. Questions about life outside of work in the past 7 days

F1. Outside of the healthcare setting/your workplace, have you been in close contact with a confirmed COVID-19 patient or a person with COVID-19 symptoms?	☐ Yes ☐ No ☐ Unknown
F2. How many times have you used public transportation besides a family car (public bus, train)?	☐ 0 ☐ 1-2 ☐ 3-5 ☐ 5-8 ☐ 9 or more
F3. How many times have you attended a social indoor social event or gathering with MORE than 10 people? (This includes activities such as attending church/other house of	☐ 0 ☐ 1-2 ☐ 3-5

worship, parties, weddings, and sporting events, or visiting a bar or restaurant).	☐ 5-8 ☐ 9 or more
F4. How often have you worn a mask when in an indoor setting outside of your home?	☐ always ☐ often ☐ sometimes ☐ rarely ☐ never ☐ did not go to indoor locations outside home
F5. How often have you stayed at least 2 metres from other people in indoor spaces outside your home?	☐ always ☐ often ☐ sometimes ☐ rarely ☐ never ☐ did not go to indoor locations outside home
F6. How many times have people who do not live in your household visited your home?	☐ always ☐ often ☐ sometimes ☐ rarely ☐ never
F7. How many times have you visited other people in their homes?	☐ always ☐ often ☐ sometimes ☐ rarely ☐ never ☐ did not go to indoor locations outside home

Recent Symptoms:

In the past (7) days, have you experienced any of the following symptoms (check all that apply):

- ☐ Fever
- ☐ Cough
- ☐ General Weakness
- ☐ Fatigue
- ☐ Headache
- ☐ Muscle aches
- ☐ Sore Throat
- ☐ Runny Nose
- ☐ Shortness of Breath
- ☐ Lack of Appetite
- ☐ Nausea
- ☐ Vomiting
- ☐ Diarrhea
- ☐ Altered Mental Status
- ☐ Loss of Taste
- ☐ Loss of Smell

If yes to any of symptoms:

Date of onset of first symptom: _____

Did you see a doctor for your symptoms?

- ☐ Yes
- ☐ No

Did you go to an emergency room?

- ☐ Yes
- ☐ No

Did you get hospitalized for your symptoms?

- ☐ Yes
- ☐ No

Did you get tested for SARS-CoV-2?

- ☐ Yes
- ☐ No

If yes, what test was done, check all that apply:

- ☐ Rapid test (Nasal Swab)
- ☐ PCR (Nasal Swab)
- ☐ Blood test
- ☐ Xray or CT scan

What were the results?

- ☐ Covid-19 Positive
- ☐ Covid-19 Negative

Weekly symptom follow-up questionnaire

Have you received the COVID-19 vaccine?

- ☐ Yes I have received two does of COVID vaccine
- ☐ Yes I have received only one dose of COVID vaccine
- ☐ No I have not received any doses of COVID vaccines

In the past 7 days, or since you last filled out this questionnaire, have you received the COVID-19 Vaccine?

- ☐ Yes
- ☐ No

1. If yes, what was the date of the dose? (dd/mm/yyyy)	___/___/___
2. Which vaccine did you receive? (product name)	List options
3. Mode of vaccine ascertainment (to be the verified by study staff)	☐ = vaccination card ☐ = vaccination registry ☐ = self-report ☐ = other (specify_____) ☐ = not documented
4. What was the Batch of the vaccine received?	Please provide the match number from the above documents or state ☐ Unknown

For women, when you received the vaccine, were you pregnant?

- ☐ Yes (if yes, specify trimester)
- ☐ No

In the past (7) days, have you experienced any of the following symptoms (check all that apply):

- ☐ Fever
- ☐ Cough
- ☐ General Weakness
- ☐ Fatigue

- ☐ Headache
- ☐ Muscle aches
- ☐ Sore Throat
- ☐ Runny Nose
- ☐ Shortness of Breath
- ☐ Lack of Appetite
- ☐ Nausea
- ☐ Vomiting
- ☐ Diarrhea
- ☐ Altered Mental Status
- ☐ Loss of Taste
- ☐ Loss of Smell
- ☐ I have not experienced any of these symptoms in the past 7 days or since I last filled out this questionnaire

If yes to any of symptoms:

Date of onset of first symptom: _____

Did you see a doctor for your symptoms?

- ☐ Yes
- ☐ No

Did you go to an emergency room?

- ☐ Yes
- ☐ No

Did you get hospitalized for your symptoms?

- ☐ Yes
- ☐ No

Did you get tested for SARS-CoV-2?

- ☐ Yes
- ☐ No

If yes, what test was done, check all that apply:

- ☐ Rapid test
- ☐ PCR Nasal Swab
- ☐ Blood test

☐ Xray or CT scan

What were the results?
☐ Covid-19 Positive
☐ Covid-19 Negative

Questions about life outside of work in the past 7 days

F1. Outside of the healthcare setting/your workplace, have you been in close contact with a confirmed COVID-19 patient or a person with COVID-19 symptoms?	☐ Yes ☐ No ☐ Unknown
F2. How many times have you used public transportation besides a family car (public bus, train)?	☐ 0 ☐ 1-2 ☐ 3-5 ☐ 5-8 ☐ 9 or more
F3. How many times have you attended a social indoor social event or gathering with MORE than 10 people? (This includes activities such as attending church/other house of worship, parties, weddings, and sporting events, or visiting a bar or restaurant).	☐ 0 ☐ 1-2 ☐ 3-5 ☐ 5-8 ☐ 9 or more
F4. How often have you worn a mask when in an indoor setting outside of your home?	☐ always ☐ often ☐ sometimes ☐ rarely ☐ never ☐ did not go to indoor locations outside home
F5. How often have you stayed at least 2 metres from other people in indoor spaces outside your home?	☐ always ☐ often ☐ sometimes ☐ rarely ☐ never ☐ did not go to indoor locations outside home
F6. How many times have people who do not live in your household visited your home?	☐ always ☐ often ☐ sometimes ☐ rarely ☐ never
F7. How many times have you visited other people in their homes?	☐ always ☐ often ☐ sometimes ☐ rarely ☐ never ☐ did not go to indoor locations outside home

Questionnaire for following up ad hoc symptomatic participants

In last 7 days, have you had any of the following symptoms (check all that apply):

- ☐ Fever
- ☐ Cough
- ☐ General Weakness
- ☐ Fatigue
- ☐ Headache
- ☐ Muscle Aches
- ☐ Sore Throat
- ☐ Runny Nose
- ☐ Shortness of Breath
- ☐ Lack of Appetite
- ☐ Nausea
- ☐ Vomiting
- ☐ Diarrhea
- ☐ Altered Mental Status
- ☐ Loss of Taste
- ☐ Loss of Smell
- ☐ Other

If yes to any of symptoms:

Date of onset of first symptom: _____

If the participant has had symptoms in the past 7 days that meet the case definition (see below), a respiratory specimen should be collected and the participant should be instructed to quarantine until test results are available, in according with Albania Ministry of Health and Social Protection guidelines.

A participant should be considered a suspected case of COVID-19 for this study if the following criteria are met

- Acute (in the previous 7 days) onset of fever or cough OR
- acute onset of one or more of the following symptoms in the previous 7 days: General weakness/fatigue, headache, myalgia, sore throat, coryza, dyspnoea, anorexia/nausea/vomiting, diarrhoea, altered mental status, anosmia, ageusia.

Questionnaire for following up positive COVID-19 cases 30 days after positive test

Since the day of your positive test (xxx Date), how many days were you sick for?

- ☐ ___ days
- ☐ I am still feeling ill

If you are still feeling ill, which of the following symptoms do you have?

- ☐ Fever
- ☐ Cough
- ☐ General Weakness
- ☐ Fatigue
- ☐ Headache
- ☐ Muscle Aches
- ☐ Sore Throat
- ☐ Runny Nose
- ☐ Shortness of Breath
- ☐ Lack of Appetite
- ☐ Nausea
- ☐ Vomiting
- ☐ Diarrhea
- ☐ Altered Mental Status
- ☐ Loss of Taste
- ☐ Loss of Smell
- ☐ Other

During the course of your COVID-19 illness, did you see a doctor for your symptoms?

- ☐ Yes
- ☐ No

During the course of your COVID-19 illness, did you go to an emergency room?

- ☐ Yes
- ☐ No

Did you get hospitalized for your COVID-19 illness?

- ☐ Yes
- ☐ No

If yes, how many days were you hospitalized for:

- ☐ __ XX days
- ☐ Still hospitalized

Did you receive oxygen for your symptoms?

- ☐ Yes
- ☐ No

Did you require ICU care?

- ☐ Yes
- ☐ No

Did you require intubation?

- ☐ Yes
- ☐ No

For participants who were hospitalized during the course of their illness, staff should record if at the 30-day questionnaire the participant was

- ☐ Still in hospital
- ☐ Discharged from hospital
- ☐ Deceased

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	10-12
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-8
Bias	9	Describe any efforts to address potential sources of bias	5, 15
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	10
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	5, 12
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	12
Outcome data	15*	Report numbers of outcome events or summary measures over time	n/a

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n/a
Discussion			
Key results	18	Summarise key results with reference to study objectives	13-14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-057741.R1
Article Type:	Protocol
Date Submitted by the Author:	20-Jan-2022
Complete List of Authors:	Sridhar, Shela; Boston Children's Hospital, Global Health Program Fico, Albana; Institute of Public Health Preza, Iria; Institute of Public Health Hatibi, Iris; Institute of Public Health Sulo, Jonilda; Southeast European Center for Surveillance and Control of Infectious Disease Kissling, Esther ; Epiconcept SAS Daja, Rovena; Institute of Public Health Ibrahim, Rawi; WHO Regional Office for Europe Lemos, Diogo; WHO Regional Office for Europe Rubin-Smith, Julia; Boston Children's Hospital Schmid, Alexis; Boston Children's Hospital Vasili, Adela; Institute of Public Health Valenciano, M; EpiConcept Jorgensen, Pernille; World Health Organization, Regional Office for Europe; Pebody, Richard; World Health Organization Regional Office for Europe Lafond, Kathryn; CDC Atlanta Katz, Mark ; World Health Organization Regional Office for Europe Bino, Silvia; Institute of Public Health, Southern European Centre for Surveillance and Control of Infectious Diseases (SECID)
Primary Subject Heading:	Public health
Secondary Subject Heading:	Infectious diseases, Global health, Health policy
Keywords:	COVID-19, Infection control < INFECTIOUS DISEASES, Public health < INFECTIOUS DISEASES

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

Current Manuscript Word Count (not including title, references, tables/figures): 3798

Abstract word count: 300

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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 behaviors. 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 piece-wise proportional hazards model (VE = 1 - hazard ratio [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 enrollment, 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 enrollment. 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 (IPH) 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.

Registration: This study has been registered with ClinicalTrials.gov (NCT04811391).

Strengths and limitations of this study

- This study is a rigorous, prospective vaccine effectiveness study using standardized 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 to the general population, which may limit the generalizability 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.

Introduction

COVID-19 vaccination is critical to reducing the impact of the COVID-19 pandemic. While randomized controlled trials (RCTs) of COVID-19 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, 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] have been published on real-world VE in low- 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 January 11, 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 Immunization (SAGE) and the European Technical Advisory Group, the Albanian National Immunization Technical Advisory Group prioritized health workers (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 January 2021 and the first doses of COVID-19 vaccine were administered to healthcare 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 hospitalized 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 enrollment.

Methods and analysis

Objectives

The study is a 12-month prospective longitudinal cohort study, which started in 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 health workers. 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 health workers, 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 enroll 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 enrollment. 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 enrollment

Each participant will be followed for 12 months. After the initial ethical approval, the study was publicized 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. Health workers 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 enrollment questionnaire that included demographic, clinical, and epidemiological information, information about vaccination history, occupation- and community-related behavior, and recent symptoms. The date of receipt of the first Covid vaccine, for participants who were vaccinated prior to enrollment, was also collected (see 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 RT-PCR testing to evaluate for asymptomatic SARS-CoV-2 infection at the time of enrollment. Participants were not blinded to data collectors. However, individuals performing the analysis receive only de-identified information.

For study participants who did not receive their first COVID-19 vaccine at or prior to enrollment but receive their first COVID-19 vaccine 14 days or more after enrollment, 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 enrollment 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 (Appendix 2). Timing of questionnaires is outlined in Table 2.

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 Institute of Public Health, 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 (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 information system for infectious diseases, 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 (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 enrollment, blood samples for serology are collected at 3, 6, 9 months, and 12 months after enrollment, in order to identify new SARS-CoV-2 infections during the study period.

Study staff

The study team includes staff of the Albanian Institute of Public Health (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 health workers 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 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%,[14] 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, TN, USA) , a secure web application for building and managing online surveys and databases.[15] Within REDCap, a specific project containing all data collection

instruments including participant consent forms, enrollment questionnaires, specimen collection, laboratory results, weekly questionnaires and follow up of symptomatic and COVID-19 positive cases are customized for this study and organized 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 are conducted following IPH guidelines on the proper handling and processing of potentially infectious biological materials, based on the latest recommendations from WHO.[16] Dedicated medical staff collect nasal swabs from participants at enrollment 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.[17] RT-PCR- positive specimens collected from participants

will be further characterized by genetic sequencing at a regional reference laboratory in Europe, following WHO guidelines.[18] in order to understand whether changes in VE could be due in part to virus mutations or specific variant viruses.

Enrollment 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.[19] Cut-offs were determined according to manufacturer instructions.[19] Serology samples from enrollment 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 anti-spike 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

Vaccine effectiveness 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.

Hazard ratios comparing vaccinated and unvaccinated will be estimated using piece-wise exponential survival models. Poisson regression will be used to model these,[20] 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 – hazard ratio [HR]). Follow-up will be from enrollment to the earliest of outcome or study exit. Primary VE analysis will be for the hazard ratio 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 to 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 vs. fully vaccinated;
- type of HW and wards;
- age groups;
- sex;

- presence or absence of high-risk conditions for severe illness (see appendix 1);[11]
- study week or weeks of the year;
- time since vaccination
- variants of concern

Baseline data

The study began recruitment on Feb 19, 2021, and as of May 1, 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 enrollment 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 co-morbidity. In all, 1434 of 1504 (95%) reported having direct patient contact. 536 (36%) reported having tested positive for COVID-19 prior to enrollment (418 (77%) by PCR, 54 (10%) by serology, 47 (9%) by rapid test and 46 (7%) were unsure of the testing method). At enrollment, 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 enrollment, 7 out of 18 reported at least 1 symptom. Overall, 842 (56%) of study participants had received one dose of the Pfizer BNT162b2 mRNA COVID-19 vaccine at enrollment. All vaccinated participants received their first vaccine dose no more than 4 days prior to enrollment. No participant had received two doses of vaccine prior to enrollment, and no participant received a vaccine other than the Pfizer BNT162b2 mRNA COVID-19 vaccine prior to enrollment.

Ethics and dissemination

The study protocol and procedures were reviewed and approved by the WHO Ethical Review Board, reference number CERC.0097A as well as the IPH institutional review board, reference number 156. All

data is stored in REDCap and stakeholders have user-specific defined access. All participants have provided written informed consent.

This study has been registered with ClinicalTrials.gov (Identifier NCT04811391). A manuscript with the results of the primary study will be published in a peer-reviewed journal.

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 US and Israel.[4,5,21] Effectiveness may vary in lower-resource settings, in part due to challenges such as vaccine transport, storage, administration and associated technical skill.[3] Low- and middle-income countries could also face varying levels of virus transmission, in part due to lower vaccine coverage, and different circulating viruses. As of January 11, over 460,000 people (41% of the population) in Albania had received at least one dose of COVID-19 vaccine,[22] much lower than the one-dose coverage rates in the United Kingdom (76%), the United States of America (73%) and Israel (72%) by the same date.[22] Understanding VE in a middle-income country such as Albania provides important information regarding allocation and effective vaccine distribution in similar contexts. This understanding has a critical impact on local funding of vaccines as well as building trust in local vaccine rollouts.[23]

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.[21]

The enrollment 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 enrollment, a figure that is higher than the 48% seropositivity reported from a seroprevalence survey of the general population of Tirana, Albania during December 2020,[24] 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%.[25]

While previously infected study participants are likely to be at reduced risk for reinfection for at least 5-6 months,[26] 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 anti-nucleocapsid 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.[27,28,29]

A strength of our study is the novelty of conducting a rigorous, prospective VE study using standardized 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 enrollment, 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 to the general population. As a result, study results are not be generalizable 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 re-infection 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 vaccine effectiveness for mild and, to a lesser extent severe, illness.[29] 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,[26] we may be inadequately powered to evaluate secondary VE objectives such as VE by age and co-morbidity 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.

Data Availability Statement: No additional data available.

Disclaimer: The authors alone are responsible for the views expressed in this article and they do not necessarily represent the views, decisions or policies of the institutions with which they are affiliated.

Contributors: All authors made substantial contributions to the conception or design of the work, as well as the acquisition, analysis and interpretation of data for the work. Shela Sridhar, Iris Hatibi, Jonilda Sulo, Esther Kissling, Kathryn Lafond, Mark Katz, and Slivia Bino were involved in the conceptualization, analysis and interpretation of the work as well as primary drafting of this manuscript. Albana Fico, Pernille Jorgensen, Diogo Lemos, Marta Valenciano Richard Pebody and Rawi Ibrahim were involved in the conceptualization of this work and final drafting of this manuscript. Iria Preza, Rovena Daja, Julia Rubin-Smith, Alexis Schmid, and Adela Vasili were involved in the conceptualization, acquisition, analysis and interpretation of this work as well as the final drafting of this manuscript. All authors were involved in drafting and revising the document for intellectual content and provided final approval of the version to be published. All authors are in agreement to be accountable for all aspects of this work in regards to accuracy and integrity.

Competing interests: There are no competing interests to report.

Funding: The study is funded by the WHO Regional Office for Europe the United States Centers for Disease Control and Prevention (US CDC) and conducted by the Institute of Public Health (IPH) in Albania. There is no associated award/grant number.

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Table 1. Knowledge gaps of Cohort Study to Measure COVID-19 Vaccine Effectiveness among Health Workers in Albania (COVE-AL), 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 re-infection of SARS CoV-2.	We will evaluate the incidence of SARS-CoV-2 re-infection among previously infected health care workers comparing vaccinated to unvaccinated individuals.
The utility of COVID-19 vaccine to prevent re-infection 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.

Table 2: Timing of questionnaires and specimen collection, Cohort Study to Measure COVID-19 Vaccine Effectiveness among Health Workers in Albania (COVE-AL)

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

Table 3: Case Definition for Suspected symptomatic Covid-19 illness, Cohort Study to Measure COVID-19 Vaccine Effectiveness among Health Workers in Albania (COVE-AL)

- 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	• Diarrhea
• 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	

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, 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)

Table 4: Sociodemographic and clinical Characteristics, vaccination status, and SARS-CoV-2 serological status of Participants at Enrollment, Cohort Study to Measure COVID-19 Vaccine Effectiveness among Health Workers in Albania (COVE-AL)

Smoking	
Current or previous smoker	273 (14)
Never smoked	1231 (86)
Occupation	
Nurse	691 (46)
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)
Enrollment PCR Results	
Positive	18 (1)
Negative	1486 (99)
Enrollment Serology Results	
Positive	1085 (72)
Negative	414 (28)
Cut-off (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).

Enrollment Questionnaire

INSTRUCTIONS:
This survey will take about 5-10 minutes to complete. If you have any questions, please contact [XXXXX] at [-XXXXXXXX] or email XXXXXX.
Thank you again for your time.

A. Demographics, SARS-CoV-2 history and vaccination history

A1. What is your age?

A2. Are you male or female?

A2a. If you are female:

Are you pregnant?: (If yes, specify trimester)

Are you Breastfeeding?:

A3. What is your height in cm?

A4. What is your weight in kg?

A5. Have you ever been diagnosed with any of the following?

- ☐ Cancer
- ☐ Chronic Heart Disease, excluding high blood pressure
- ☐ High blood pressure/Hypertension
- ☐ Chronic Kidney Disease
- ☐ Chronic Liver Disease (such as cirrhosis, hepatitis, fatty liver disease)
- ☐ Chronic Lung Disease (such as asthma, COPD, bronchitis, etc…)
- ☐ Diabetes
- ☐ Immunocompromised, including solid organ transplant and HIV
- ☐ Neurological Disease, including cerebrovascular disease, epilepsy, multiple sclerosis, etc…
- ☐ Obesity
- ☐ Autoimmune disorder

A6. Do you currently smoke?

- ☐ Yes
- ☐ No

A6a: If no, have you smoked previously?

- ☐ Yes
- ☐ No

A7. How many people (not including yourself) do you live with?

- ☐ 0
- ☐ 1
- ☐ 2
- ☐ 3
- ☐ 4
- ☐ 5
- ☐ 6 or more

A8. Since January 2020, have you ever received a positive laboratory test for SARS-CoV-2, the virus that causes COVID-19?

- ☐ Yes
- ☐ No

A8a. If yes, when was the positive test (date), and what kind of test was performed (PCR or rapid test or serology)

- ☐ PCR (nasal swab)
- ☐ Rapid Test (nasal swab)
- ☐ Serology Test (a blood test)
- ☐ Don't remember

Date of Test _____

(Allow option for multiple positive test results)

COVID 19 Vaccination Questions

A9. When the COVID -19 vaccine becomes available, what are the chances that you will choose to receive a COVID-19 vaccination if you are offered one?

- ☐ Almost Zero Chance
- ☐ Very Small Chance
- ☐ Small
- ☐ Moderate
- ☐ Large
- ☐ Very Large Chance

☐ Almost Certain
☐ I have already received a COVID-19 vaccine: Date: _____

Vaccination history **COVID vaccine**	
1. Do you have a contraindication for the COVID-19 vaccine?	☐ Yes ☐ No ☐ Unknown
2. Have you received the first dose of any COVID-19 vaccine?	☐ Yes ☐ No ☐ Unknown
3. If yes, what was the date of the first dose? (dd/mm/yyyy)	___/___/___
4. Which vaccine did you receive? (product name)	
5. Mode of vaccine ascertainment (to be the verified by study staff)	☐ = vaccination card ☐ = vaccination registry ☐ = self-report ☐ = other (specify_____) ☐ = not documented
6. What was the Batch of the vaccine received?	Please provide the match number from the above documents or state ☐ Unknown
7. Have you received a second dose of the COVID-19 vaccine?	☐ Yes ☐ No ☐ Unknown
8. If yes, what day did you receive the second dose (dd/mm/yyyy)	___/___/___
9. Which kind of vaccine did you receive for the second dose (product name)	
10. What was the Batch number of the second dose vaccine you received?	Please provide the match number from the ascertainment documents or state ☐ Unknown
11. Mode of vaccine ascertainment of the second dose (to be verified by study staff)	☐ = vaccination card ☐ = vaccination registry ☐ = self-report ☐ = other (specify_____)

	☐ = not documented

Did you receive the influenza vaccine in the past winter (since September 2020)?

☐ Yes
☐ No

B. Occupation and Work Responsibilities

B1. In what departments, wards, or parts of your health facility do you regularly work? Check all that apply.

☐ Hospital
☐ Emergency Department
☐ Critical Care or Intensive Care Unit
☐ Infectious Diseases
☐ Lung diseases
☐ Internal Medicine and/or Medical Specialties
☐ Pediatrics and/or Pediatric Specialties
☐ Surgery and/or Surgical Specialties
☐ Gynecology and/or Obstetrics
☐ Oncology and/or Hematology
☐ Dentistry
☐ Radiology
☐ Outpatient clinic
☐ Pharmacy
☐ Laboratory
☐ Nutrition
☐ Social Assistance
☐ Physiotherapy
☐ Occupational therapy
☐ *Other*

B1a:_Other department or ward, please SPECIFY: _____

B2. What is your current job/occupation at the hospital?

☐ Nurse
☐ Medical doctor
☐ Midwife

- ☐ Laboratory technician
- ☐ Biologist
- ☐ Pharmacist
- ☐ Janitorial staff
- ☐ Food worker
- ☐ Social Worker
- ☐ Radiology Technician
- ☐ *Other*

B3. With which groups of patients do you have regular or daily face-to-face contact? Check all that apply.

- ☐ Infants aged <1 year
- ☐ Children aged 1-12 years
- ☐ Teenagers aged 13-19
- ☐ Adults aged 20-64
- ☐ Older adults aged 65 and older
- ☐ Pregnant women

B4. Are you a clinical health worker (such as a doctor, nurse, or medical technician) who provides hands-on medical care to patients?

- ☐ Yes
- ☐ No

B4a. [If B4= "Yes"] Do you perform any of the following procedures regularly (on most workdays)? This means you do this task yourself (and not simply oversee). Check any or all that apply.

- ☐ Collect a respiratory specimen using a swab
- ☐ Collect a sputum specimen
- ☐ Administer medication using a nebulizer
- ☐ Apply nasal cannula (two pronged tube for nasal oxygen)
- ☐ Apply oxygen face mask
- ☐ Perform tracheal intubation
- ☐ Insert a nasogastric (feeding) tube
- ☐ Perform manual ventilation
- ☐ Apply mechanical ventilation

- ☐ Perform suction of fluids or secretions
- ☐ Perform chest physiotherapy (such as chest percussion)
- ☐ Perform bedside bronchoscopy

C. Health Status

C1. How would you describe your current health overall?

- ☐ Excellent
- ☐ Very Good
- ☐ Good
- ☐ Fair
- ☐ Poor

E. Questions about Illness, Vaccines, and Missing Work

E1. How much do you know about the Covid-19 vaccine?

- ☐ Nothing at all
- ☐ A little
- ☐ Some
- ☐ A lot
- ☐ A great deal

E2. COVID-19 vaccination is safe.

- ☐ Strongly agree
- ☐ Mildly agree
- ☐ Neutral
- ☐ Mildly disagree
- ☐ Strongly disagree

E3. If you are unable to or don't get a COVID-19 vaccination, what do you think your chance of getting the COVID-19 will be?

- ☐ Almost Zero Chance
- ☐ Very Small Chance
- ☐ Small
- ☐ Moderate
- ☐ Large
- ☐ Very Large Chance

E4. How effective do you think the COVID-19 vaccine is in preventing you from getting sick with COVID-19?

- ☐ Extremely effective
- ☐ Very effective
- ☐ Somewhat effective
- ☐ Not too effective
- ☐ Not at all effective

E5. If you get a COVID-19 vaccination, what do you think your chance of getting sick with COVID-19 will be this year…?

- ☐ Almost Zero Chance
- ☐ Very Small Chance
- ☐ Small Chance
- ☐ Moderate Chance
- ☐ Large Chance
- ☐ Very Large Chance

E6. If I get an COVID-19 vaccination, I will be less likely to miss work because of getting sick with COVID-19.

- ☐ Strongly agree
- ☐ Mildly agree
- ☐ Neutral
- ☐ Mildly disagree
- ☐ Strongly disagree

E7. Compared to your co-workers at your health facility, how favorable or unfavorable is your attitude toward COVID-19 vaccination?

- ☐ Extremely more favorable
- ☐ Much more favorable
- ☐ Slightly more favorable
- ☐ Average for co-workers at my facility
- ☐ Slightly less favorable
- ☐ Much less favorable
- ☐ Extremely less favorable

E8. If I don't get a COVID-19 vaccination, I will regret it.

- ☐ Strongly agree

☐ Mildly agree
☐ Neutral
☐ Mildly disagree
☐ Strongly disagree

E9. How worried are you about getting sick with COVID-19 during the next 12 months?

☐ Extremely worried
☐ Very worried
☐ Moderately worried
☐ A little worried
☐ Not at all worried

E10. I get sick with influenza and other respiratory viruses more easily than other people my age.

☐ Strongly agree
☐ Mildly agree
☐ Neutral
☐ Mildly disagree
☐ Strongly disagree

E11. Employees at my healthcare facility are encouraged to go home if they have respiratory symptoms at work.

☐ Strongly agree
☐ Mildly agree
☐ Neutral
☐ Mildly disagree
☐ Strongly disagree

F. Questions about life outside of work in the past 7 days

F1. Outside of the healthcare setting/your workplace, have you been in close contact with a confirmed COVID-19 patient or a person with COVID-19 symptoms?	☐ Yes ☐ No ☐ Unknown
F2. How many times have you used public transportation besides a family car (public bus, train)?	☐ 0 ☐ 1-2 ☐ 3-5 ☐ 5-8 ☐ 9 or more
F3. How many times have you attended a social indoor social event or gathering with MORE than 10 people? (This includes activities such as attending church/other house of	☐ 0 ☐ 1-2 ☐ 3-5

worship, parties, weddings, and sporting events, or visiting a bar or restaurant).	☐ 5-8 ☐ 9 or more
F4. How often have you worn a mask when in an indoor setting outside of your home?	☐ always ☐ often ☐ sometimes ☐ rarely ☐ never ☐ did not go to indoor locations outside home
F5. How often have you stayed at least 2 metres from other people in indoor spaces outside your home?	☐ always ☐ often ☐ sometimes ☐ rarely ☐ never ☐ did not go to indoor locations outside home
F6. How many times have people who do not live in your household visited your home?	☐ always ☐ often ☐ sometimes ☐ rarely ☐ never
F7. How many times have you visited other people in their homes?	☐ always ☐ often ☐ sometimes ☐ rarely ☐ never ☐ did not go to indoor locations outside home

Recent Symptoms:

In the past (7) days, have you experienced any of the following symptoms (check all that apply):

- ☐ Fever
- ☐ Cough
- ☐ General Weakness
- ☐ Fatigue
- ☐ Headache
- ☐ Muscle aches
- ☐ Sore Throat
- ☐ Runny Nose
- ☐ Shortness of Breath
- ☐ Lack of Appetite
- ☐ Nausea
- ☐ Vomiting
- ☐ Diarrhea
- ☐ Altered Mental Status
- ☐ Loss of Taste
- ☐ Loss of Smell

If yes to any of symptoms:

Date of onset of first symptom: _____

Did you see a doctor for your symptoms?

- ☐ Yes
- ☐ No

Did you go to an emergency room?

- ☐ Yes
- ☐ No

Did you get hospitalized for your symptoms?

- ☐ Yes
- ☐ No

Did you get tested for SARS-CoV-2?

- ☐ Yes
- ☐ No

If yes, what test was done, check all that apply:

- ☐ Rapid test (Nasal Swab)
- ☐ PCR (Nasal Swab)
- ☐ Blood test
- ☐ Xray or CT scan

What were the results?

- ☐ Covid-19 Positive
- ☐ Covid-19 Negative

Weekly symptom follow-up questionnaire

Have you received the COVID-19 vaccine?

- ☐ Yes I have received two does of COVID vaccine
- ☐ Yes I have received only one dose of COVID vaccine
- ☐ No I have not received any doses of COVID vaccines

In the past 7 days, or since you last filled out this questionnaire, have you received the COVID-19 Vaccine?

- ☐ Yes
- ☐ No

1. If yes, what was the date of the dose? (dd/mm/yyyy)	___/___/___
2. Which vaccine did you receive? (product name)	List options
3. Mode of vaccine ascertainment (to be the verified by study staff)	☐ = vaccination card ☐ = vaccination registry ☐ = self-report ☐ = other (specify_____) ☐ = not documented
4. What was the Batch of the vaccine received?	Please provide the match number from the above documents or state ☐ Unknown

For women, when you received the vaccine, were you pregnant?

- ☐ Yes (if yes, specify trimester)
- ☐ No

In the past (7) days, have you experienced any of the following symptoms (check all that apply):

- ☐ Fever
- ☐ Cough
- ☐ General Weakness
- ☐ Fatigue
- ☐ Headache

- ☐ Muscle aches
- ☐ Sore Throat
- ☐ Runny Nose
- ☐ Shortness of Breath
- ☐ Lack of Appetite
- ☐ Nausea
- ☐ Vomiting
- ☐ Diarrhea
- ☐ Altered Mental Status
- ☐ Loss of Taste
- ☐ Loss of Smell
- ☐ I have not experienced any of these symptoms in the past 7 days or since I last filled out this questionnaire

If yes to any of symptoms:

Date of onset of first symptom: _____

Did you see a doctor for your symptoms?

- ☐ Yes
- ☐ No

Did you go to an emergency room?

- ☐ Yes
- ☐ No

Did you get hospitalized for your symptoms?

- ☐ Yes
- ☐ No

Did you get tested for SARS-CoV-2?

- ☐ Yes
- ☐ No

If yes, what test was done, check all that apply:

- ☐ Rapid test
- ☐ PCR Nasal Swab
- ☐ Blood test
- ☐ Xray or CT scan

What were the results?

☐ Covid-19 Positive

☐ Covid-19 Negative

Questions about life outside of work in the past 7 days

F1. Outside of the healthcare setting/your workplace, have you been in close contact with a confirmed COVID-19 patient or a person with COVID-19 symptoms?	☐ Yes ☐ No ☐ Unknown
F2. How many times have you used public transportation besides a family car (public bus, train)?	☐ 0 ☐ 1-2 ☐ 3-5 ☐ 5-8 ☐ 9 or more
F3. How many times have you attended a social indoor social event or gathering with MORE than 10 people? (This includes activities such as attending church/other house of worship, parties, weddings, and sporting events, or visiting a bar or restaurant).	☐ 0 ☐ 1-2 ☐ 3-5 ☐ 5-8 ☐ 9 or more
F4. How often have you worn a mask when in an indoor setting outside of your home?	☐ always ☐ often ☐ sometimes ☐ rarely ☐ never ☐ did not go to indoor locations outside home
F5. How often have you stayed at least 2 metres from other people in indoor spaces outside your home?	☐ always ☐ often ☐ sometimes ☐ rarely ☐ never ☐ did not go to indoor locations outside home
F6. How many times have people who do not live in your household visited your home?	☐ always ☐ often ☐ sometimes ☐ rarely ☐ never
F7. How many times have you visited other people in their homes?	☐ always ☐ often ☐ sometimes ☐ rarely ☐ never ☐ did not go to indoor locations outside home

Questionnaire for following up ad hoc symptomatic participants

In last 7 days, have you had any of the following symptoms (check all that apply):

- ☐ Fever
- ☐ Cough
- ☐ General Weakness
- ☐ Fatigue
- ☐ Headache
- ☐ Muscle Aches
- ☐ Sore Throat
- ☐ Runny Nose
- ☐ Shortness of Breath
- ☐ Lack of Appetite
- ☐ Nausea
- ☐ Vomiting
- ☐ Diarrhea
- ☐ Altered Mental Status
- ☐ Loss of Taste
- ☐ Loss of Smell
- ☐ Other

If yes to any of symptoms:

Date of onset of first symptom: _____

If the participant has had symptoms in the past 7 days that meet the case definition (see below), a respiratory specimen should be collected and the participant should be instructed to quarantine until test results are available, in according with Albania Ministry of Health and Social Protection guidelines.

A participant should be considered a suspected case of COVID-19 for this study if the following criteria are met

- Acute (in the previous 7 days) onset of fever or cough OR
- acute onset of one or more of the following symptoms in the previous 7 days: General weakness/fatigue, headache, myalgia, sore throat, coryza, dyspnoea, anorexia/nausea/vomiting, diarrhoea, altered mental status, anosmia, ageusia.

Questionnaire for following up positive COVID-19 cases 30 days after positive test

Since the day of your positive test (xxx Date), how many days were you sick for?

- ☐ ___ days
- ☐ I am still feeling ill

If you are still feeling ill, which of the following symptoms do you have?

- ☐ Fever
- ☐ Cough
- ☐ General Weakness
- ☐ Fatigue
- ☐ Headache
- ☐ Muscle Aches
- ☐ Sore Throat
- ☐ Runny Nose
- ☐ Shortness of Breath
- ☐ Lack of Appetite
- ☐ Nausea
- ☐ Vomiting
- ☐ Diarrhea
- ☐ Altered Mental Status
- ☐ Loss of Taste
- ☐ Loss of Smell
- ☐ Other

During the course of your COVID-19 illness, did you see a doctor for your symptoms?

- ☐ Yes
- ☐ No

During the course of your COVID-19 illness, did you go to an emergency room?

- ☐ Yes
- ☐ No

Did you get hospitalized for your COVID-19 illness?

- ☐ Yes
- ☐ No

If yes, how many days were you hospitalized for:

- ☐ __ XX days
- ☐ Still hospitalized

Did you receive oxygen for your symptoms?

- ☐ Yes
- ☐ No

Did you require ICU care?

- ☐ Yes
- ☐ No

Did you require intubation?

- ☐ Yes
- ☐ No

For participants who were hospitalized during the course of their illness, staff should record if at the 30-day questionnaire the participant was

- ☐ Still in hospital
- ☐ Discharged from hospital
- ☐ Deceased

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	10-12
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-8
Bias	9	Describe any efforts to address potential sources of bias	5, 15
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	10
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	5, 12
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	12
Outcome data	15*	Report numbers of outcome events or summary measures over time	n/a

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n/a
Discussion			
Key results	18	Summarise key results with reference to study objectives	13-14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.