PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	COVID-19 vaccine effectiveness among health-care workers in Albania (COVE-AL): protocol for a prospective cohort study and cohort baseline data
AUTHORS	Sridhar, Shela; Fico, Albana; Preza, Iria; Hatibi, Iris; Sulo, Jonilda; Kissling, Esther; Daja, Rovena; Ibrahim, Rawi; Lemos, Diogo; Rubin-Smith, Julia; Schmid, Alexis; Vasili, Adela; Valenciano, M; Jorgensen, Pernille; Pebody, Richard; Lafond, Kathryn; Katz, Mark; Bino, Silvia

VERSION 1 – REVIEW

REVIEWER	Ana Junqueira-Kipnis Federal University of Goiás Biosciences Special Academic Unit
REVIEW RETURNED	29-Oct-2021

GENERAL COMMENTS	Revision for BMJ Open The study: Cohort Study to Measure COVID-19 Vaccine Effectiveness among Health Workers in Albania (COVE-AL): Study Protocol and Description of Participants at Enrollment, presents a protocol of an ongoing study to evaluate the COVID-19 vaccine efficacy among Health Workers in 3 hospitals in Albania. Additionally, the study presents the participants demographics and some analysis regarding COVID-19 vaccinations among the recruited participants. The study protocol was approved by WHO. The scientific integrity and the credibility of the study data is substantially dependent on the study design and methodology, thus some points should be clarified. General comments: The text needs grammar revision. i.e. “Participants are complete weekly symptom questionnaires”. Also, the trial is ongoing then the verbal time is wrong throughout the text. Major concerns: 1. It was not mentioned the blindness or CODE regarding the participants identity. 2. It is not clear how the authors will perform the statistic analysis if ~80% of the participants were COVID-19 seropositive and this might reduce the number of COVID-19 cases through the study. Please provide the alternative statistic test. Protection induced by vaccination plus previous seropositivity to COVID-19 may indicate that the study will not be completed due to the reduced number of COVID-19 cases during the period of one year. Please provide an alternative for the trial completion.

REVIEWER	Catherine Fry Drug Safety Research Unit
REVIEW RETURNED	15-Dec-2021

GENERAL COMMENTS	This is a well designed study which addresses important questions regarding the Covid-19 vaccine effectiveness in health workers in a middle-income country. I only have suggestions of minor revisions to be made: 1) I would recommend that the manuscript is reviewed throughout for minor grammatical/wording errors, of which I have identified several. For example: - Page 4, line 3, remove 'are' from 'Participants are complete...' - Page 5, 3rd bullet point, add in 'infected' to read 'previously infected individuals' - Page 5, 3rd bullet point, remove 'and' after comma. - Page 8, first line under the title 'Study Design', remove comma after 'participants' - Page 12, line 1, add 'swabs' after 'nasal' 2) On page 4, lines 1-2 for the sentence beginning 'Serology samples...' it may be helpful to make it clearer that this sentence relates to baseline. 3) On page 5, the 2nd bullet point needs rewording to clarify that the PCR testing is not to be carried out at regular intervals/will only identify infections at baseline or when symptomatic. 4) On page 6, I was unsure as to what the reason was for including 2 different population estimates (2.8 million/2.9 million)? Would it be best to stick to the most recent data here? 5) On page 6, line 12, I am wondering whether it is just high rates of morbidity that have been reported in HWs - have high rates of mortality also been reported? 6) On page 8, under the title 'Study Design', the second sentence needs rewording for clarification. This should probably be two separate sentences. 7) Throughout the paper and questionnaires, the first and second dose are talked about, but will there be inclusion of the booster vaccine? 8) On page 12, the final sentence in the first paragraph regarding treatment of serum specimens needs rewording for clarification - perhaps remove 'sera spun and'.

VERSION 1 – AUTHOR RESPONSE

Reviewer #1 Comments

The scientific integrity and the credibility of the study data is substantially dependent on the study design and methodology, thus some points should be clarified.

General comments: The text needs grammar revision. i.e. “Participants are complete weekly symptom questionnaires”. Also, the trial is ongoing then the verbal time is wrong throughout the text.

Thank you for your comments.

We have reviewed the manuscript and corrected the grammatical errors.

Our enrollment tenses are in the past tense, because at the time of writing this manuscript enrollment had been completed. The remainder of the manuscript was written in present or future tense depending on the context. We have attempted to clarify this with our wording.

Major concerns:
1. It was not mentioned the blindness or CODE regarding the participants identity.

Thank you for this comment. We have added the following statement about blindness to the first line of the "study design" section. It now reads as follows: Participants were not blinded to data collectors. However, individuals performing the analysis receive only de-identified information

2. It is not clear how the authors will perform the statistic analysis if ~80% of the participants were COVID-19 seropositive and this might reduce the number of COVID-19 cases through the study. Please provide the alternative statistic test.

Under the "Analysis plan and statistical considerations: Vaccine effectiveness analysis" section, we have clarified in the following statement in the analysis, under the section, that the analysis will be carried out for the overall cohort and again separately for participants with and without previous infection using the same analytic approach:

"Analyses will be carried out in the overall cohort and separately among participants with and without previous infection, using the same analytic approach."

While we will use the same analytic approach, we have acknowledged in the limitations section that the fact that a high percentage of the HWs in our study were previously infected at the time of enrollment may limit the power of our study to determine VE in a previously uninfected population.

However, as we have mentioned in this same section "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 re-infections, and meaningfully reduced vaccine effectiveness for mild and, to a lesser extent, severe illness. 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."

Protection induced by vaccination plus previous seropositivity to COVID-19 may indicate that the study will not be completed due to the reduced number of COVID-19 cases during the period of one year. Please provide an alternative for the trial completion.

While there may be a reduced number of COVID-19 cases in the study, as we mentioned above, recent data have indicated that there is an increased likelihood of reinfection, particularly with the omicron variant. In addition, there are variables other than the attack rate that also impact power calculations, such as vaccine coverage and vaccine effectiveness, that are beyond our control. As a result, we currently plan to maintain the current study for one year. Because enrollment occurred over a nearly 3-month period, the total duration of the study will be about 15 months in order to accommodate those who were enrolled later. However, no participant will participate for more than 12 months.

Reviewer #2 Comments

1) I would recommend that the manuscript is reviewed throughout for minor grammatical/wording errors, of which I have identified several. For example:
- Page 4, line 3, remove 'are' from 'Participants are complete...'
- Page 5, 3rd bullet point, add in 'infected' to read 'previously infected individuals'
- Page 5, 3rd bullet point, remove 'and' after comma.
- Page 8, first line under the title 'Study Design', remove comma after 'participants'
- Page 12, line 1, add 'swabs' after 'nasal'

Thank you for these corrections. We have made all of these corrections in the revised document, and we have reviewed the document for additional grammatical errors.

2) On page 4, lines 1-2 for the sentence beginning 'Serology samples...' it may be helpful to make it clearer that this sentence relates to baseline.

Thank you. We have revised this sentence so that it now reads as follows: 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.

3) On page 5, the 2nd bullet point needs rewording to clarify that the PCR testing is not to be carried out at regular intervals/will only identify infections at baseline or when symptomatic.

Thank you. We have reworded this bullet point for clarity so that it now reads as follows: 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.

4) On page 6, I was unsure as to what the reason was for including 2 different population estimates (2.8 million/2.9 million)? Would it be best to stick to the most recent data here?

Thank you. This was a mistake. We have removed the second reference to the population size, and left one reference to the population (2.9 million).

5) On page 6, line 12, I am wondering whether it is just high rates of morbidity that have been reported in HWs - have high rates of mortality also been reported?

Thank you for this point. Some evidence suggesting high rates of mortality among HWs has been reported. We have therefore added "mortality" to this sentence.

6) On page 8, under the title 'Study Design', the second sentence needs rewording for clarification. This should probably be two separate sentences.

Thank you. We have reworded and split this sentence, so it now reads as follows: . 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.

7) Throughout the paper and questionnaires, the first and second dose are talked about, but will there be inclusion of the booster vaccine?

Thank you for this comment. If participants receive additional doses of vaccine, these doses will be considered in the analysis. We have added this sentence to the "Analysis plan and statistical considerations" section.

8) On page 12, the final sentence in the first paragraph regarding treatment of serum specimens needs rewording for clarification - perhaps remove 'sera spun and'.

Thank you. We have clarified this sentence. It now reads as follows: Serum specimens are separated from whole blood and stored and shipped at 4 °C, or the sera are 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.

VERSION 2 – REVIEW

REVIEWER	Catherine Fry Drug Safety Research Unit
REVIEW RETURNED	03-Feb-2022

GENERAL COMMENTS	Thank you for addressing the previous comments. I would recommended that this paper is accepted following one minor revision:

	- Under 'Recruitment and Enrollment', the sentence that has been added on blinding and those conducting the analysis receiving anonymised information would be better placed in the 'Study Design' section of the manuscript.