PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	SARS-CoV-2 antibody responses post-vaccination in UK healthcare workers with pre-existing medical conditions: a cohort study
AUTHORS	Ward, Victoria; Wei, Jia; Gordon, William; Barnes, Eleanor; Dunachie, Susie; Jeffery, Katie; Eyre, David; O'Donnell, Anne-Marie

VERSION 1 – REVIEW

REVIEWER	Hoxha, Ilir Dartmouth Institute for Health Policy and Clinical Practice
REVIEW RETURNED	09-Aug-2022

GENERAL COMMENTS	General reactions ⁾ Thank you for the opportunity to review this manuscript. The manuscript looks at antibody response based on serological testing of health care workers in four teaching hospitals in the Oxford area. Overall I find this study very well designed and presented. I also find it a valuable contribution and interesting. I have minor specific comments below which may help authors and editors with further fine-tuning and development of the manuscript. ⁾ I think that information which is already there can be organized a bit better. ⁾ Sometimes part of the text in the results section seem to belong to the methods section. (Example: "A total of 5,968 HCWs had serological data available between 9 April 2020 and 26 August 2021, among which 1,635 HCWs had anti-spike IgG measurements 14-84 days post second vaccination and provided data on any underlying health conditions; these HCWs were included in the study." belongs in sample selection of the study population. ⁾ Or the sequence of presentation of information. For example in methods section, statistical analysis, the outcome was after details that I could consider secondary (i.e. control variables). I have this impression for all sections of the manuscript. ⁾ Maybe introducing additional subheadings may help. Or reorganization of text. Abstract How did you decide to use linear regression? Strengths and limitations Do they present best the paper… am not sure… (Page 4, Line 4) I am not sure if I would use the word "cohort" in the last point… "study population" would seem more appropriate to me. Methods

	⁾ Methods seem robust and the section seems to present all relevant data. ⁾ How did the authors decide to use linear regression? ⁾ Am not sure if I understand how risk score was used in the design of this study and analysis. ⁾ A short description of risk assessment tool may help to understand… ⁾ Stat analysis starts with variables that could be used for control… not that clear presentation of outcome variables… and variables used to examine the effect as well as control variables. ⁾ Sample inclusion process in form of chart and clearer description in the text of methods could be helpful… Results Authors state “A total of 5,968 HCWs had serological data available between 9 April 2020 and 26 August 2021,” Why this is different from the time when the test were applied 23 April to 30 June? Also see it in the methods section. Discussion Would extend on these two points: What the implications of your study? How your study is comparable, with other studies in UK, or other countries?

REVIEWER	Kul , Gülnur Kırıkhan State Hospital
REVIEW RETURNED	12-Sep-2022

GENERAL COMMENTS	It is a valuable study on the antibody responses that occur after vaccination in the long-lasting COVID 19 pandemic all over the world. According to the results of the study, it managed to reduce the occupational exposure of people who may be at high risk by estimating the antibody responses that may occur in healthcare workers. The study design is a retrospective observational study. Therefore, there was no homogeneous distribution among the groups. It was not possible to compare demographic characteristics and comorbidities between groups according to antibody levels. In addition, the risk factors associated with low antibody levels mentioned in the first paragraph of the discussion section are known as risk factors not only for healthcare workers but also for all vaccinated individuals. It is recommended to correct the relevant sentence in this direction. In the third paragraph of the discussion section, two different vaccine types were compared. Since the number of participants who received two doses of astra zeneca vaccine was approximately 20 % of the study population, this comparison will be incorrect because the distributiın is not homogenus. In the fourth paragraph of the Discussion section, the relationship between obesity and antibody levels is explained by the increased risk of serious disease. However, short-term antibody responses are not associated with increased disease risk. It is a valuable work that can be published if corrections are made on the issues I mentioned above.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Ilir Hoxha, Dartmouth Institute for Health Policy and Clinical Practice
Comments to the Author:
General reactions
⎫ Thank you for the opportunity to review this manuscript. The manuscript looks at antibody response based on serological testing of health care workers in four teaching hospitals in the Oxford area. Overall I find this study very well designed and presented. I also find it a valuable contribution and interesting. I have minor specific comments below which may help authors and editors with further fine-tuning and development of the manuscript.

⎫ I think that information which is already there can be organized a bit better.
⎫ Sometimes part of the text in the results section seem to belong to the methods section. (Example: "A total of 5,968 HCWs had serological data available between 9 April 2020 and 26 August 2021, among which 1,635 HCWs had anti-spike IgG measurements 14-84 days post second vaccination and provided data on any underlying health conditions; these HCWs were included in the study." belongs in sample selection of the study population.

Response: We have moved this description under 'Participants and settings' subheading in the Methods section.

⎫ Or the sequence of presentation of information. For example in methods section, statistical analysis, the outcome was after details that I could consider secondary (i.e. control variables). I have this impression for all sections of the manuscript.

Response: We have moved the description of the outcome variable before the description of the covariates to make the sequence of presentation better.

⎫ Maybe introducing additional subheadings may help. Or reorganization of text.

Response: We have added subheadings of 'Outcome', 'Covariates', and 'Statistical analysis' within the Methods section.

Abstract
How did you decide to use linear regression?
Response: Because antibody level is a continuous variable, and we wanted to examine the association between antibody levels with different explanatory variables. We model the response on a log10 scale, as this is common practice in similar studies of antibody response.

Strengths and limitations
Do they present best the paper… am not sure…
(Page 4, Line 4) I am not sure if I would use the word "cohort" in the last point… "study population" would seem more appropriate to me.
Response: We have changed it to 'study population'.

Methods
⎫ Methods seem robust and the section seems to present all relevant data.
⎫ How did the authors decide to use linear regression?

Response: Because antibody level is a continuous variable, and we wanted to examine the association between antibody levels with different explanatory variables. We model the response on a log10 scale, as this is common practice in similar studies of antibody response.

⎫ Am not sure if I understand how risk score was used in the design of this study and analysis.
⎫ A short description of risk assessment tool may help to understand…

Response: The ALAMA COVID-age risk score was calculated based on age, sex, ethnicity, and presence of comorbidities for each HCW. A score ≥85 indicates very high vulnerability, 70-84 high

vulnerability, 50-69 moderate vulnerability, and <50 low vulnerability. Using this risk score as an exposure variable to examine its association with antibody levels, we can understand whether HCWs with higher vulnerability to SARS-CoV-2 infection generated lower antibody levels post vaccination. We have included a paragraph of description of the risk score in the 'Covariates' section.

⁾ Stat analysis starts with variables that could be used for control… not that clear presentation of outcome variables… and variables used to examine the effect as well as control variables.
⁾ Sample inclusion process in form of chart and clearer description in the text of methods could be helpful…

Response: We have changed the sequence of description in the 'Statistical analysis' section, and added additional subheadings for better presentation. We have added a sample inclusion chart as suggested (Figure S1).

Results
Authors state "A total of 5,968 HCWs had serological data available between 9 April 2020 and 26 August 2021," Why this is different from the time when the test were applied 23 April to 30 June? Also see it in the methods section.
Response: Routine PCR testing for symptomatic staff started from 27 March 2020. PCR and serological testing for asymptomatic staff started from 23 April 2020. Some staff had earlier serological testing as part of routine occupational health care, which also continued after routine asymptomatic testing stopped, we have clarified this in the methods text: "Additional serological testing of HCWs was undertaken by the Occupational Health department based on clinical assessment (results are included from 9 April 2020 onwards)."

Discussion
Would extend on these two points:
What the implications of your study?
Response: We have expanded our discussion on the study implications in the last paragraph.

How your study is comparable, with other studies in UK, or other countries?
Response: We found that antibody levels post-vaccination were lower in ChAdOx1 recipients and HCWs with comorbidities, especially immunosuppression or organ transplantation. These results were consistent with previous literature that people with comorbidities had lower antibody levels. We have added further references and expanded our discussion on comparison with previous studies.

Reviewer: 2
Gülnur Kul , Kırıkhan State Hospital
Comments to the Author:
Dear author
It is a valuable study on the antibody responses that occur after vaccination in the long-lasting COVID 19 pandemic all over the world. According to the results of the study, it managed to reduce the occupational exposure of people who may be at high risk by estimating the antibody responses that may occur in healthcare workers.

The study design is a retrospective observational study. Therefore, there was no homogeneous distribution among the groups. It was not possible to compare demographic characteristics and comorbidities between groups according to antibody levels.

Response: Our study is representative of healthcare workers as a group, and so we agree with the reviewer that the distribution of demographic characteristics and co-morbidities may not be representative of the general population. We acknowledge this in our discussion. However, that said, we are able to compare antibody levels across different groups within the HCW population by demographics and comorbidities, Tables 1 and 2 provide descriptive details and the regression models presented provide adjusted estimates on the importance of these characteristics.

In addition, the risk factors associated with low antibody levels mentioned in the first paragraph of the discussion section are known as risk factors not only for healthcare workers but also for all vaccinated individuals. It is recommended to correct the relevant sentence in this direction.
Response: We have removed ‘in HCWs’.

In the third paragraph of the discussion section, two different vaccine types were compared. Since the number of participants who received two doses of astra zeneca vaccine was approximately 20 % of the study population, this comparison will be incorrect because the distributiın is not homogenus.

Response: Using the regression approach adopted it is possible to compare antibody levels between vaccines even with differences in the number of HCWs receiving each vaccine type. To provide reassurance that the populations receiving each vaccine type were broadly similar we have compared these below, a slightly higher proportion of ChAdOx1 recipients were female (87% vs 81%), but otherwise the groups are very similar:

Two ChAdOx1 vaccinations (N=387) Two BNT162b2 vaccinations(N=1234) p value
Age 0.6
Median 46 45.5
Q1, Q3 34.000, 55.500 33.000, 56.000
Sex 0.003
Female 338 (87.3%) 997 (80.8%)
Male 48 (12.4%) 237 (19.2%)
Non-disclosed 1 (0.3%) 0 (0.0%)
Ethnicity 0.3
Asian 69 (17.8%) 234 (19.0%)
Black 18 (4.7%) 31 (2.5%)
Mixed 10 (2.6%) 26 (2.1%)
Not stated 4 (1.0%) 17 (1.4%)
Other 10 (2.6%) 45 (3.6%)
White 276 (71.3%) 881 (71.4%)
BMI 0.7
<16 1 (0.3%) 2 (0.2%)
16-24.9 169 (43.7%) 522 (42.3%)
25-29.9 129 (33.3%) 384 (31.1%)
30-34.9 59 (15.2%) 201 (16.3%)
35-39.9 16 (4.1%) 67 (5.4%)
40+ 13 (3.4%) 58 (4.7%)
Comorbidity 0.3
No 217 (56.1%) 649 (52.6%)
Yes 170 (43.9%) 585 (47.4%)
Evidence of Covid-19 infection at baseline 0.2
No 307 (79.3%) 1030 (83.5%)
Yes 80 (20.7%) 204 (16.5%)
Covid Age Score 0.2
Median 50 50
Q1, Q3 35.000, 57.000 35.000, 60.000

In the fourth paragraph of the Discussion section, the relationship between obesity and antibody levels is explained by the increased risk of serious disease. However, short-term antibody responses are not associated with increased disease risk.
Response: In our analysis we didn’t find an association between peak antibody levels with BMI, so we compared our results to a recent study in which vaccinated people with obesity had a faster waning of vaccine-induced immunity compared with normal weight people, and thus associated with increased hospitalization and mortality from breakthrough infections. We have rephrased our original description to make it clearer.

It is a valuable work that can be published if corrections are made on the issues I mentioned above.