Author's response to reviews

Title: Sero-prevalence and risk factors for Hepatitis B infection among health care workers in a tertiary Hospital in Uganda

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Version: 5 Date: 24 March 2010

Author's response to reviews: see over
January, 27th, 2010

Editor-in-Chief,
BMC Infectious Diseases Journal

MS: 1630543822968744- Sero-prevalence and risk factors for Hepatitis B infection among health care workers in a tertiary Hospital in Uganda

Dear Editor,

In response to your email of November 12, 2009, we are pleased to submit a revised version of the above mentioned manuscript point by point as raised by the reviewers.

Editorial request:
Copyediting: We recommend that you copyedit the paper to improve the style of written English.

Response to editorial request:
We are happy to inform you that the whole paper has been copyedited and we believe it is in a much better shape.

Reviewer 1: Simone Lanini

Reviewer’s comment:

Abstract
1. Discretionary Revision (page 2-3): The abstract should provide key information that enables to understand the objective of a study, assess its value and decide whether to read the article.
In particular:
• Background lacks of a clear cut statement about the objective of the study;
• Methods does not report some relevant data about the study design (i.e.: type of study; timing; overall population & groups and the statistical model.
• Results gives only proportion but no frequencies;
• Conclusion: Ok

Response to reviewer’s comment on abstract:
The abstract has been revised to include information on the study objective, design, population and analytical methods. To avoid crowding the abstract, we deliberately left out frequencies but gave the overall sample size so that frequencies can be derived if the reader wanted to. We feel this makes it more reader friendly.

Reviewer’s comment:

Background
2. Discretionary Revision (page 4) “On the other hand, infected HCW pose a risk of transmitting the virus to the patients they attend to [12-15]”. This is true but irrelevant for this study since HCW-to-patient transmission was not considered in
Response to reviewer’s comment:
We agree with the reviewer, this sentence has been completely removed from the text.

Reviewer’s comment:

3. Minor compulsive (page 4-5) : Does “HB” stand for “HBV”? If yes please use only one acronym (i.e. HBV) to refer to the same item in the text.

Response to reviewer’s comment:
This has been revised (removed HB and replaced it with HBV) as advised to ensure consistence.

Reviewer’s comment:

4. Minor compulsive (page 4) “The differences in HB infection rates reflect the disparities in the risk of exposure to infection [18, 19]. For instance one study conducted among dental students and dentists revealed that a significantly higher proportion of dentists tended to use gloves compared to the dental students [20], while another study showed that 38% of professional HCW were vaccinated compared to only 3.5% of the housekeeping staff in the same hospital[21].” I cannot understand what do you mean with “HB infection rate”. Is that the prevalence of anti-HBc (i.e.: the marker of natural infection) or the prevalence of HBsAg (i.e.: the prevalence of HBV carrier) or the overall incidence of infection among these populations.

Response to reviewer’s comment:
What was being referred to as “HB infection rate” is either of the two depending on what is reported in a given study; anti-HBc or HBsAg. Studies have reported differences in prevalence of both markers by HCW cadre.

Reviewer’s comment:

5. Minor compulsive(page 5): “This study aimed at contributing to the discourse by determining the prevalence and risk factors for hepatitis B infection and also assessed infection prevention strategies availability including vaccination.” The study does not contain any assessment of intervention nor does it assess any prevention strategy. Please eliminate the second part of this statement or give the original data of your assessment.

Response to reviewer’s comment:
It is not clear what the reviewer means by “there was no assessment of intervention or prevention strategy”. Routinely health care facilities are expected to have a minimum of infection prevention protocols in the work place including disinfection of equipment and work surfaces, use of protective gear (gloves, aprons etc), and vaccinations. Participants were asked about their use of gloves, other protective gear, perception of quality of disinfection, and vaccination. This in no way was exhaustive but adequate to have an idea of the IP situation in the facility. It should be emphasized that the assessment was not for a specific infection control but rather routine workplace prevention practices that implicitly relate to HBV infection prevention as well.

the study.

Response to reviewer’s comment:
We agree with the reviewer, this sentence has been completely removed from the text.
Reviewer’s comment:

Study design, sampling and participant recruitment
6. Minor compulsive (page 6): being this a cross sectional study authors should give the timing of sampling i.e.: the dates when the first and last HCWs were interviewed and sampled. In fact, in order to evaluate potential biases, it is very relevant to understand if the sampling was performed throughout a small period (e.g weeks) or over a long time (e.g. years).

Response to reviewer’s comment:
I guess the reviewer means participant recruitment when he says “timing of sampling”. Participant recruitment took approximately two months March-April 2003. This detail has been added to the text.

Reviewer’s comment:

7. Minor compulsive(page 6): “The strata were based on health care worker cadre thus; specialists, medical officers, paramedical officers, laboratory technicians, and nurses/midwives (nurses, midwives, nursing assistants and theatre attendants)”.
This list does not fit with le list in table 1 (i.e.: doctor, clinical/dental officer, nurse, midwives, laboratory technician and nursing assistant). Please use the same classes in the text and the tables.

Response to reviewer’s comment:
The former and latter categories alluded to above are in fact very similar. One was used for sampling and the other for analytical purposes. At analysis, categories can always be collapsed as long as they make sense for example “specialists” and “medical officers” are all doctors and were rightfully analysed as such.

Reviewer’s comment:

Measurements
8. Major compulsive (Page 7): outcome should be redefined according to the HBV natural history “The main outcome variables were hepatitis B surface antigen (HBsAg), Hepatitis B surface antibody (Anti-HBs) and hepatitis B core antibody (Anti-HBc). Their presence indicates immunity to HB infection following an infection or immunization with hepatitis B vaccine. Anti-HBc is directed against the core antigen and its presence indicates a present or past infection”. The definition of the outcomes represent the major drawback of the study which makes it not completely scientifically sound. In particular it must be bear in mind that, if taken apart from each other, the test results of Ab/Ag systems does NOT represent the clinical outcomes of the HBV infection. To define the clinical outcomes you need to consider patterns of positivity/negativity. In my opinion, and given the study design, authors may define 2 different types of outcomes i.e.: clinical outcomes, that can be used for the descriptive epidemiology, and an exposure outcomes that can be used in the estimate of risk of infection. The Ab/Ag patterns to define the clinical outcomes of HBV infection are not a matter of discussion. Given the systems tested and the results obtained these can only be:
• Recovered from natural infection = anti-HBs + / anti-HBc +;
• Immune after immunization = anti-HBs + / anit-HBc-;
• Current infection (i.e.: acute hepatitis; chronic hepatitis and HBsAg carries) = HBsAg + / anti-HBc+;
• Unexposed susceptible: negative to all Ab/Ag systems.
With regard to exposure outcomes (or markers of exposures) and risk calculation you may define patients as:
• Exposed (either whit or without a current infection): anti-HBc positive;
• Unexposed = anti-HBc negative.
Moreover to calculate the risk of infection after exposure you should not consider the immune after vaccination patients since they are not a risk of infection whichever their exposure (see below point 11 and 12)

Response to reviewer’s comment:
The reviewer’s comments and suggestions have been taken into consideration while revising this section. HBsAg, Anti-HBs and Anti-HBc have been referred to as serologic markers not outcomes to avoid creating the impression that they stand alone. The distribution of the serologic markers by socio-demographic characteristics remains as it was in table 2. We emphasize that these are individual markers not clinical outcomes.

Table 3 has the clinical outcomes alluded to by the reviewer. This table was in the earlier version of the paper but has been revised to reflect the reviewer’s advice but also keeping in line with published literature on the interpretation of HB markers and a reference has been given.

Former Table 4 has been split into table 4 and 5. We felt that it would be important to capture the risk factors for “current infection” and “life time exposure to HB infection” hence the two tables. The table contents changed a bit because the models were re-estimated as per advice given.
The “immune after vaccination” were excluded while estimating risk as advised.

Reviewer’s comment:

9. Minor compulsive(page 7): the authors should state which type antiHBc antibodies were tested (i.e.: IgM; IgG; total-Ab).

Response to reviewer’s comment:
The anti-HBc referred to in the paper refers to total anti-HBc. This has been highlighted in the paper for clarity.

Reviewer’s comment:

Laboratory investigations
10. Minor compulsive(page 7-8): “The HBsAg test was considered positive if the optical density was equal or greater than the cut off. Samples giving an absorbance of equal to or greater than the mean absorbance of the cut off control(10 mIU/ml were considered positive for Anti-HBs. Samples that gave an absorbance equal or less than the cut off value were considered positive for anti-HBc.”
This is irrelevant. When using a commercial standardized system you are expected to use the interpretation given by the manufacturer. If this is the case you should delete this part and say
that results are according the manufacturer’s interpretation. If this is not the case you should explain why you are not using a standardized interpretations.

Response to reviewer’s comment:
The interpretation of lab results was according to the manufacturer’s guidelines. We have deleted the unnecessary details as recommended.

Data analysis
11. Major compulsive: the risk analysis for exposure should be redefined using the outcomes given at point 8.

Response to reviewer’s comment:
Risk analysis has been revised to have two outcomes: i) life time exposure to infection and ii) current infection.

Reviewer’s comment:

12. Major compulsive: patient tested anti-HBs pos. / anti-HBc neg. must be not considered in the risk estimation model since they were not at risk whichever the exposure (i.e.: not susceptible)

Response to reviewer’s comment:
These have been excluded while re-estimating the models

Reviewer’s comment:

13. Minor compulsive (page 8): you should state the cut-off the statistical significance you considered both for univariate and multivariate logistic regression (i.e.: p<0.05 or p<0.01).

Response to reviewer’s comment:
The cut off for level of significance for multivariate regression was p<0.05, however for bivariate analysis, we used 10% for inclusion such variables in the logistic regression models.

Reviewer’s comment:

14. Minor compulsive (page 8): you should state the statistical test you used to assess the significance at the univariate analysis. Moreover if you used a parametric test, such as X-square, you should also demonstrate that your sample recognize a normal distribution.

Response to reviewer’s comment:
The odds ratios and p values for the bivariate analysis have been included in both table 4 & 5.

Reviewer’s comment:
15. Discretionary Revision (page 8): “Factors that were significantly associated to the risk of the sero-markers at bivariate analysis (results not shown) or those that have been reported in the literature to be associated with hepatitis B infection were analyzed in a logistic regression model controlling for the individual socio-demographic characteristics.”.
In my opinion the two-step approach (i.e.: univariate + multivariate analysis) you have used is one of best way to carry out a MLR model. Therefore I do not think that it is a good idea to include all the risk factors you can find in literature. You might have much better results using a limited set of variable rather than using a huge MLR model. If appropriate you can also decide to set the p-value cut-off in the univariate analysis, to include variables in MLR, at an higher value such as 0.1. Moreover it would be more transparent if you show in the tables the results of univariate analysis.

Response to reviewer’s comment:
The authors feel that the approach used is appropriate and the models are not over specified. Certainly we didn’t include all variables reported in the literature to be associated with HBV infection but it would also be unrealistic to leave all of them out of the model just because they were not significant at bivariate analysis. We have however removed about three variables from each model.

Reviewer’s comment:
Results
Risk of exposure at work place
16. Minor compulsive (Page 9):“Risk of exposure to potentially infectious body fluids at the work place was assessed using a set of variables as shown in Table 1.”
This table shows data about descriptive analysis (i.e. type of exposure, vaccinal status, use of personal protective device and risk perception) and not data about risk estimate. Please correct the test.

Response to reviewer’s comment:
The use of the term risk here meant potential for exposure to patient body fluids not “risk estimate”. To avoid confusion however, we have replaced “risk” with “potential”.

Reviewer’s comment:
17. Discretionary Revision (page 9):”Over 65% of respondents think that the work place and surfaces are not adequately disinfected mainly due to limited availability of disinfectants (results not shown).”
It should be considered among the risk perception since this is referred data and not an objective evaluation.

Response to reviewer’s comment:
The two issues, although all concern perception, refer to different measures. We asked about their perception of safety of work place and also asked about their personal perceived risk of getting infected with hepatitis B infection. “Risk perception” in table 1 has been replaced with “perceived risk of infection”
Reviewer’s comment:

18. Major compulsive (page 9) “Consistent use of gloves during procedures as a means of preventing risk of infection was reported in 55% of respondents.” Authors should define in methods section what they consider to be “consistent use” and give appropriate reference.

Response to reviewer’s comment:
Consistent use of gloves was a self reported response to refer to the use of gloves each time they carried out a procedure involving patient body fluids. We didn’t have an objective way of measuring and validating it but relied on what they perceive to be their routine practice in work place.

Reviewer’s comment:

Vaccination against Hepatitis B

19. Major compulsive (page 10): “Only 6% of respondents had been vaccinated against hepatitis B infection.” Some points should be better addressed:
• I cannot understand how the figure of 6% comes out. Authors should better define, in the methods section, how did you investigate the vaccinal status (i.e.: by asking to the HCWs, by reviewing HCWs’ medical sheets for vaccination etc.).

Response to reviewer’s comment:
In the methods section we highlighted that we used a questionnaire to collect information on history of HB vaccination “HB vaccination status” among other things. Since this wasn’t one of the main outcomes, we didn’t feel that we should state the question asked in the methods section. However for your information, respondents were asked whether they have ever been vaccinated against hepatitis B and if yes, how many doses were received. Note that childhood vaccination in Uganda only began in 2002 and health care workers are not routinely vaccinated. We therefore believe that those who have had the opportunity to be vaccinated should be able to recall this with some degree of accuracy.

Reviewer’s comment:

• Authors should consider that after being vaccinated only 2 outcome are possible success (i.e.: antiHBsAg+/antiHBc-) or failure (i.e.: antiHBsAg+/antiHBc-). Since the actual proportion of subject effectively vaccinated is 3% (i.e.: 3% = 1.1%+1.9%; see remarks point 8). You should argument in the discussion section why the effectiveness of vaccination is only about 50%.

Response to reviewer’s comment:
From the data collected we know that about 35% of those vaccinated got the three doses. That means that some of those with less than 3 doses got immunity. This point has been highlighted in the discussion section.

Reviewer’s comment:

• Being this retrospective data where exposure (i.e.: asking about vaccinal status) was assessed after subjects sero-status induction (i.e. vaccination) authors must consider the effect
of recall bias. For example 7 subject were tested antiHBsAg+/antiHBc-; they reported to be not vaccinated but in fact they were.

Response to reviewer’s comment:
*True recall bias could play a role in the reports, although we believe is likely to be minimal given that HB vaccination is rarely given and is paid for. There can however also be other competing explanations related to the test results such as a false anti-HBc negative.*

Reviewer’s comment:

20. Minor compulsive (page 10): “Overall about 26% (21.6-30.7%; 95% CI) of all participants had antibodies against hepatitis B virus.”
Please say which HBV Ab you are referring to (i.e.: antiHBs or antiHBc).

Response to reviewer’s comment:
*This has been corrected. Reference was to anti-HBs*

Reviewer’s comment:

21. Major compulsive (page 11): “With the exception of the category of doctors and other Christians, categories which had a high prevalence of HBsAg also had a high prevalence of anti-HBs.”
I cannot understand what does it mean. In general subjects infected during the adulthood have about 90% chance to clear infection by producing antiHBs Ab.
Do you have any evidence that “doctors” and “other Christian” are more likely than other in clearing infection?

Response to reviewer’s comment:
*I don’t know whether I understand the reviewers concern here. This was an observation and description of the results (proportions) as they are, not association or causation of sorts. It is only fair that results contrary to our expectation should be reported even without a definite explanation of the observation. This is the very reason why such variables were included in the multivariate models. This statement has however been deleted from the text.*

Reviewer’s comment:

22. Major compulsive (page 11): “About 42% (36.8-47.1; 95% CI) had evidence of previous hepatitis B infection.”
This is not scientifically sound. The only universal serological marker of previous contact with HBV either cleared infection, HBV-carriers or active infection are the anti-HBc antibodies whose proportion in your study 44.3% (see point 8).

Response to reviewer’s comment:
*This has been corrected in the text and revisions made on table 3.*

Reviewer’s comment:
23. Major compulsive (page 11): “Seven (7) cases -category “d” Table 3 were found to be anti-HBs positive and anti-HBC negative and yet reported that they had never been vaccinated. For purposes of classification these were treated as “immune after infection”. This is not scientifically sound please see previous remarks at points 8 and consider the possibility of recall bias. Please remember that, with only very rare exceptions among subjects with occult B hepatitis or severely immune-compromised patients, all subjects who experienced a HBV infection are anti-HBc positive.

Response to reviewer’s comment:
We have taken the reviewers advice and categorised these as “Immune after vaccination”

Reviewer’s comment:

24. Major compulsive (page 11): “Only 1% of all participants were immune against hepatitis B secondary to vaccination.”
This is not scientifically sound please see previous remarks at points 8 (the actual proportion is about 3%).

Response to reviewer’s comment:
This is related to point 23 above. After the revision the percentage is 3%.

Reviewer’s comment:

Risk factors for Hepatitis B infection
25. Major compulsive (page 12-13): I believe you need to re-write this part according to clear outcomes (i.e.: exposed and unexposed according to the anti-HBc status; see point 8). In my opinion the study design is not suitable to define the risk of chronic infection (i.e.: risk to be HBsAg pos.).

Response to reviewer’s comment:
The results in this section have been re-written to reflect the changes in the table 4 and 5. We took advice of assessing risk factors for exposure (anti-HBc), but we also felt that is reasonable to look at risk factors for current infection (HBsAg+ and anti-HBc +).

Reviewer’s comment:

26. Minor compulsive (page 12-13): As a general remark for all this section you should not report all the “not significant” association, in fact they do not reach the significance so that you cannot infer about them.

Response to reviewer’s comment:
We did not report all the non-significant associations but just a few and indeed specifically indicated that the association was not significant at 5% level.

Reviewer’s comment:

27. Minor Compulsive (page 12) “After controlling for other covariates in a logistic regression model, a number of variables were found to be significantly associated with hepatitis B infection at 5% level of significance (Table 4).”
The confidence limits should be put in methods section; moreover if you are using a multivariate (or multilogistic) regression model you needn’t say that you are controlling “for other variable” that’s implicit in a multivariate approach.

Response to reviewer’s comment:
Correction made in text

Reviewer’s comment:

Discussion
28. Major compulsive (page 12-13): I believe discussion should be re-write according to the new clinical/exposure outcomes and the new analysis of risks.(see point 8, 11, 12)

Response to reviewer’s comment:
The discussion section has been re-written accordingly.

Reviewer’s comment:

29. Major compulsive (page 12-13): Authors should give some data about base-line prevalence of antiHBc and HbsAg in the general population, according to specific age class, and discuss whether or not the difference between the general population and the sample of HCW are relevant.

Response to reviewer’s comment:
Some figures for prevalence of HBs and anti-HBc in the general population have been referred to in the discussion, reference number 6.

Reviewer’s comment:

Limitation
30. Major compulsive: authors should discuss how and if specific cross-sectional bias (i.e. temporal and incidence-prevalence bias) had affected the observation.
31. Major compulsive: authors should define and discuss if and how other possible bias, such as recall bias, selection bias etc had affected their observation.

Response to reviewer’s comment:
A discussion on potential bias has been added to the discussion

Reviewer’s comment:

32. Major compulsive (page 16): “Some categories of health care workers generally have few staff such as the dental and laboratory categories.”
If this is true you should have used exact logistic regression which is in the STATA-10 pack.
If this is the case you need to say it in methods section and specify which p-value and/or OR was calculated with the median unbiased estimates (MUE) in the tables.

Response to reviewer’s comment:
We took the reviewer’s advice on using exact logistic regression. However even increasing the computing memory to 1GB, the memory remained insufficient for the computation-only
running up to about 20 cases! The literature on exact logistic regression indicates that it is useful in studies with small sample sizes and typical examples given are in the order of 30-50 observations. With our sample size of 370, we may not really need to use the exact logistic regression method, besides we don’t have the computing capacity.

Reviewer’s comment:

Table
Table 1 should be re-written according to remarks at point 16. Please put proportions and frequency in the table.

Response to reviewer’s comment:
The frequencies have been added although we felt that to avoid crowding the table if the N and percentages are given as we did, then the frequencies can be derived if the reader wanted to.

Reviewer’s comment:

Table 2 should be re-edited according to outcomes at point 8 (i.e.: recovered after natural infection; immune after immunization; current infection; unexposed susceptible). Please put proportions and frequency in the table.

Response to reviewer’s comment:
Table 2 has been maintained as before because it does not talk about clinical outcomes but rather serological markers. Frequencies have been added to the table. Clinical outcomes are in table 3.

Reviewer’s comment:

Table 3 may be completely deleted

Response to reviewer’s comment:
This table has been revised and maintained in the paper

Reviewer’s comment:

Table 4 should be re-written according to the data of new analysis using only 1 outcome exposed/unexposed (see remark point 8, 11 and 12). It might be good reporting data of both univariate and multivariate analysis. If the table grew too big you can decide to report only significant value.

Response to reviewer’s comment:
The former table 4 is now table 4 and 5 as mentioned earlier. Contents somehow changed following re-estimation of the models

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Reviewer 2: Elisabeth Bouvet
Reviewer’s comment:
The question is well defined and pertinent. Nevertheless, study design and presentation of results are not satisfactory.
Response:
The authors have tried to re-work the study design and explanation of results more succinctly as recommended by the reviewer.

Reviewer’s comment:
There is little information on hepatitis B status among health care workers in Africa. When you read international recommendations on HCW’s protection in Africa, all of them recommend generalized vaccination against hepatitis B. Nevertheless strategy for vaccination should be determined by prevalence of hepatitis B serological markers in the population. Moreover, the risk of infection is high in community and the part of transmission related to health care is unknown and probably quite low. The situation is highly different from western countries where prevalence among general population is low.
Response:
It is true there is scanty information on hepatitis B among health care workers and in the general population in sub-Saharan Africa. In Uganda, the prevalence of HBs Ag is estimated at 10% and that for health care workers about 9%. Although many people get exposed in childhood, there still remain a large percentage of HCW (49 % in this study) who are susceptible to infection hence the need to vaccinate them.

Reviewer’s comment:
We don’t know what was the rate of random.
Response:
We don’t quite understand what the reviewer meant by “rate of random”, however assuming she was referring to random selection of participants we have attempted to explain it further here. For each stratum of HCW cadre, a proportionate random sample was drawn using computer generated random numbers:

\[
\text{Sample obtained per stratum} = \left( \frac{\text{Total number in stratum} \times \text{Sample size}}{\text{Total number of HCW (sampling frame)}} \right)
\]

We feel this last bit of the detail may not be necessary to be included in the paper.

Reviewer’s comment:
We don’t know how many people accept or refuse the survey. So finally we don’t know what is the proportion in each category of personnel who participates. The questionnaire is built as exposure to blood in hospital was the single risk factor for hepatitis B infection.
Response:
We did not keep a record of refusals, however these were very few and they were replaced by a randomly selected replacement from the same stratum of health care worker cadre as the refusal.

Reviewer’s comment:
In fact, a very surprising result is shown without explanation: individuals who have been longer in service had lower prevalence … for AgHBS which is a marker of infection acquired
during childhood. Does it mean that the risk in young generations has changed? or that people AgHbS positive are no more working in hospital because of death or complications of chronic hepatitis?

Response:
It is true and we noticed that the finding was somehow counter intuitive. We however may not be able to fully explain this observation based on our data. Nonetheless we felt it was right to report the finding.

Reviewer’s comment:
Authors should have separate prevalence of AgHBS which is more likely to be the consequence of infection acquired at birth or during childhood from infection characterized by anti Hbc +/- anti HbS more likely to be secondary to infection acquired in adult age.

Response:
From the data in our study it is not possible to discern whether current infection (marked by presence of HB surface antigen ad anti-HBc) was acquired in childhood or adulthood.

Reviewer’s comment:
I don’t agree with the introduction of religion status in risk exposure and serological analysis

Response:
Religion was included as socio-demographic variable that needs to be controlled for as it can potentially confound the relationship between HB and other known risk factors as earlier studies have shown marked variation by religion e.g, reference 6. So it was included for that reason. We don’t strongly feel that it should be removed.

Reviewer’s comment:
Tables are not easy to read and need more work to do analyses more accurate.

Response:
We have made some slight revisions on the tables for clarity and crosschecked the analysis outputs.

Reviewer’s comment:
It would have been interesting to look at serological status in a control population, for instance people working in hospital administration to get an idea of what is the part of occupational infection among all hepatitis B infections.

Response:
We agree that it would have been nice to look at comparison population especially if we were keen on proving that indeed hepatitis B infection is more prevalence among clinicians. However this was not the main focus of the paper. Besides, it is well established that HCW have an extra risk of hepatitis B infection by virtual of their work. By looking at risk factors we were interested in knowing what makes some HCW more vulnerable than others.
In summary this works brings a lot of information but the manuscript doesn’t fulfil criteria for publication. It needs to be shortened and synthesized, we need a control population, to compare Ag HBS + / Hbc + etc…

Response:
We have revised and shortened the paper where appropriate as per reviewer’s suggestion. We were however not able to introduce a control group which was not part of the original study design.

Reviewer’s comment:
A discussion on different vaccination strategies is necessary to conclude the paper.

Response:
In line with the reviewer’s suggestion we have expanded our discussion on potential vaccination strategies in the discussion section but at the same time avoided making suggestions not supported by our findings.