PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Seroprevalence of anti-SARS-CoV-2 antibodies after the first wave of the COVID-19 pandemic in a vulnerable population in France: a cross-sectional study
AUTHORS	Beaumont, Adeline; Durand, Cécile; Ledrans, Martine; Schwoebel, Valérie; Noel, Harold; Le Strat, Yann; Diulius, Donatien; Colombain, Léa; Médus, Marie; Gueudet, Philippe; Mouly, Damien; Aumaître, Hugues

VERSION 1 – REVIEW

REVIEWER	Mitchell, Hannah Queen's University Belfast
REVIEW RETURNED	07-Jul-2021

GENERAL COMMENTS	This was a very interesting study on the seroprevalence of SARS-COV-2 antibodies in socially deprived area in France. This study will be of widespread interest. I have some comments regarding the manuscript and analysis. Throughout the paper the C.I. should be consistently reported with the same notation. Throughout the manuscript the word “multivariate” is used instead of multivariable as the authors have one outcome of interest. Was ethnicity recorded or where all the participants from the gypsy population? - Authors should clearly state if all participants are from the gypsy community. Abstract Page 2 Line 18-Methods: SCoPe in full Results section: aOR- initially in full Patient and Public involvement in research Page 6 Line 25: I think there is a missing “were”? Line 29: Sentence: Then, they implemented. Line 32: Full stop needed. Statistical analysis Page 6-7 Line 8: The authors mention that they are using an adjusted Wald F test to compare the levels of seroprevalence between neighbourhoods according to individual characteristics. It is not clear as to if a logistic regression model is initially fitted to the data and then the Wald test applied to it or if univariate analysis is

	being performed. If it is the latter then other hypothesis tests should be used such as Fishers exact/ t-test depending on the data. Study population Page 7 Line 49: I am not sure what (BMI≥IOTF-30) means. It might be better to report that for those aged 6-17 years old the IOTF reference is being used and then state the cut-off point. Table 1 Page 10 Authors should add a little more information as to what analysis was performed within the table. For example is the P-value obtained from the odds ratio? General comment: Is there a possibility that individuals from Perpignan work in Spain given it is close to the Spanish border or is this unlikely and unlikely to affect the analysis?

REVIEWER	Simons, David University of London
REVIEW RETURNED	08-Sep-2021

GENERAL COMMENTS	Thank you for the opportunity to review this interesting research investigating potential risk factors for infection with SARS-CoV-2 in this special population in Southern France. This research highlights the importance of engaging with all sectors of the population when developing public health interventions, including disease surveillance, for an emerging pandemic. The authors identify high levels of seroprevalence to SARS-CoV-2 in this defined population in Perpignan, France. They conduct an acceptable sero-epidemiological survey with support from the local community and report several associations that may be of use in the implementation of future interventions. I commend the study authors on the high level of community engagement throughout the process. I have several major comments and some minor comments that I will outline below. Major comments The authors describe the randomisation of households that are invited to enroll in the study as effectively a random-walk (perhaps could benefit from a reference to formally describe this approach) they then refer to randomly selecting from one to four participants. This final step is very unclear. Did the authors recruit a pre-determined proportion of the household? Did they randomly decide whether each individual would be invited to enroll? This process is unclear within households and needs clarification to demonstrate representativeness/random recruitment. Given that household could be considered the unit of analysis within the neighborhoods and the finding of cases within households being a significant risk it would appear that analysis at the household level may be more appropriate. I defer to the statistical reviewer on this, but I would ideally like to see some input for spatial effects. The clustering of certain characteristics such as young age (families with children) and obesity within infected households could explain some of the associations seen.

	Need clearer explanation of what is included in multivariable analysis, is it just age, sex and neighbourhood? If so why only these three variable? Report age as strongly related to seropositivity but important to know whether this was explained by multigenerational households, where people >65 living in the same household as those in the higher risk groups 15-64? Minor comments Abstract: I am unsure if Gypsy community is the preferred self-designation of these communities but defer to the authors to select the most appropriate term. In several of the cited publications they are referred to Roma communities. Page 3, line 11, change contamination to prior infection. Introduction: Page 5, line 14 needs a reference line 20, in all of France to in France line 23, having work to being employed or in work line 32, The discussion on health understanding references an article which is a bit more nuanced than mentioned here (from the referenced articles (ref. 7) discussion "On the other hand, sickness is what “is seen”—a negative aspect of their personal and social life—and this is generally translated into a state of denial up to the limit. When the sickness is very severe and there are consequences, it is thus transformed into something tangible and visible, and one must therefore act.") Page 6 line 48-52, awkward wording around mentally able to participate, if individuals had to give informed consent then that would surely be the required mental criteria to attend the study location and so whether someone was physically able to attend the study site would be the inly true requirement at this stage. Univariate and multivariate should be changed to univariable and multivariable throughout as the authors are referring to the number of variables in the analysis of a single outcome measure (serological status). Page 7, line 25-26, sentence doesn;t seem to fit in the paragraph, rework. Page 7, line 37-40, change to "Samples were stored locally for a maximum of 12 hours at less than 5degrees before being transferred to the laboratory at Perpignan hospital." Page 9 line 10-12, as the seroprevalence was much higher in A than B and C it may be useful to provide a descriptive table of participant characteristics for the subsequent variables stratified by neighborhood. Page 9 line 52-53, less likely to be seropositive to have reduced odds of being seropositive, and change throughout as you are reporting odds ratios.

	Page 14 line 11-14. It does not seem reasonably to compare the prevalence in an urban population in Perpignan to a generally more rural region, it would be preferable to compare to general Perpignan prevalence if available and if not perhaps for other French cities of similar size/density. Page 14 line 22-24. The authors have not investigate the temporal association between aguesia/anosmia and infection. It is therefore not possible from these results to reference this as an early warning symptom or one that could trigger self-isolation. Page 15 line 5-8. The authors discuss the finding of lower prevalence in those that were working outside the home everyday. I agree that this is an interesting finding but without context it is difficult to question the causes of this. What were the types of work people were doing, were they high risk professions (healthcare, meatpacking, service industry) or lower risk professions (ones spending a lot of time outside)? Again this finding may be explained by not taking into account the household component of the design if generally more individuals were enrolled from households where no-one worked compare to the number of individuals enrolled from households where people worked during the lockdown. Overall I think this is important data highlighting the difficulty that public health bodies/hospitals can face in understanding infectious disease epidemiology in marginalised populations and would be a good fit for BMJ open, however, some changes are required and the manuscript would benefit from further improvements to it's style in English.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Hannah Mitchell, Queen's University Belfast Comments to the Author:
*This was a very interesting study on the seroprevalence of SARS-COV-2 antibodies in socially deprived area in France. This study will be of widespread interest. I have some comments regarding the manuscript and analysis.

Our thanks for your positive feedback. We have responded to your comments.

*Throughout the paper the C.I. should be consistently reported with the same notation.

We have changed all notations by (95% CI X to X).

*Throughout the manuscript the word “multivariate” is used instead of multivariable as the authors have one outcome of interest.

We have made the changes.

*Was ethnicity recorded or where all the participants from the gypsy population? - Authors should clearly state if all participants are from the gypsy community.

Not all participants were from the gypsy community and ethnicity was not recorded. In France, the ethnic statistics are prohibited, so we could not collect the information.
We know from several concordant sources (historical, anthropological, social) and from the participants themselves that most people in the selected neighbourhoods are from the gypsy community, but we cannot give precise statistics.

We have added the following sentence in the Method section:
“Participants were referred to the neighbourhood’s survey centre, where physicians used a standardized questionnaire in French - specifically designed for SCoPE - to collect information on the following: socio-demographic characteristics […]. Members of the Roma community were not identified in the questionnaire because of the prohibition of collection of ethnic statistics in France.”

Abstract
Page 2
*Line 18-Methods: SCoPe in full

We have modified the abstract and ‘SCoPe’ is no longer mentioned. We have added in the Methods section: “Seroprevalence of Covid-19 in Perpignan (SCoPe) is a cross-sectional seroprevalence survey […]”

*Results section: aOR- initially in full

We have made the change

*Patient and Public involvement in research Page 6 Line 25: I think there is a missing “were”?

Yes indeed, but we have deleted the sentence since it was redundant with the following sentences.

*Line 29: Sentence: Then, they implemented.
Line 32: Full stop needed.

We have made the changes.

Statistical analysis
Page 6-7
*Line 8: The authors mention that they are using an adjusted Wald F test to compare the levels of seroprevalence between neighbourhoods according to individual characteristics. It is not clear as to if a logistic regression model is initially fitted to the data and then the Wald test applied to it or if univariate analysis is being performed. If it is the latter then other hypothesis tests should be used such as Fishers exact/ t-test depending on the data.

Data reported in Table 1 are obtained from univariate logistic regressions. But all variables were previously tested by Rao-Scott X2 tests, considering the complex design.

We have modified the paragraph explaining the analyses performed:
“Seroprevalence (i.e., the proportion of seropositive individuals) was estimated with a 95% confidence interval (95% CI). Association of seroprevalence with the neighbourhood, other individual characteristics and reported symptoms was preliminary tested by univariable analysis with Rao-Scott $\chi 2$ test. Factors associated with seropositivity were then analysed using a multivariable logistic regression taking into account the sampling design. We reported odds ratios (unadjusted and adjusted) and adjusted Wald F test for significance for each variable.”

Study population
Page 7
*Line 49: I am not sure what (BMI≥IOTF-30) means. It might be better to report that for those aged 6-17 years old the IOTF reference is being used and then state the cut-off point.

There is no single cut-off point for children, it depends on age and gender. The IOTF-30 curve defines these cut-off points for obesity.
We have changed the parenthesis to: "(International Obesity Task Force (IOTF) ; BMI≥IOTF-30 cut-off points)".

Table 1
Page 10
*Authors should add a little more information as to what analysis was performed within the table. For example is the P-value obtained from the odds ratio?

We have added a note under the two tables:
Table 1: "Unadjusted odds ratio with corresponding 95% confidence intervals and p-values from univariable logistic regressions"
Table 2: "Adjusted odds ratio with corresponding 95% confidence intervals and p-values from multivariable logistic regression"
The details of the indicators under Table 1 have also been copied under Table 2.

General comment:
*Is there a possibility that individuals from Perpignan work in Spain given it is close to the Spanish border or is this unlikely and unlikely to affect the analysis?

We have not explored this hypothesis, since very few inhabitants of Perpignan work in Spain according to the population census (0.2% of occupied labour force of Perpignan). Moreover, the unemployment rate is very high in the population of these neighbourhoods.

Reviewer: 2
Dr. David Simons, University of London
Comments to the Author:
*Thank you for the opportunity to review this interesting research investigating potential risk factors for infection with SARS-CoV-2 in this special population in Southern France. This research highlights the importance of engaging with all sectors of the population when developing public health interventions, including disease surveillance, for an emerging pandemic. The authors identify high levels of seroprevalence to SARS-CoV-2 in this defined population in Perpignan, France. They conduct an acceptable sero-epidemiological survey with support from the local community and report several associations that may be of use in the implementation of future interventions. I commend the study authors on the high level of community engagement throughout the process. I have several major comments and some minor comments that I will outline below.

Thank you for your positive feedback. One of the key points of our study and other interventions in this population was indeed the engagement of all stakeholders and the community. Below you will find our responses to your comments.

Major comments
*The authors describe the randomisation of households that are invited to enroll in the study as effectively a random-walk (perhaps could benefit from a reference to formally describe this approach) they then refer to randomly selecting from one to four participants. This final step is very unclear. Did the authors recruit a pre-determined proportion of the household? Did they randomly decide whether

each individual would be invited to enroll? This process is unclear within households and needs clarification to demonstrate representativeness/random recruitment.

We used a two-stage sampling design, stratified by neighbourhood.
In the first stage, interviewers selected dwellings by systematic sampling by enumerating them while walking through a pre-determined route. In this first stage, we randomly selected the starting dwelling and the direction of the walking route using detailed map of the neighbourhoods. More details are given in the supplementary material. In a second stage, we randomly selected inhabitants in each selected household. The sampling probability was nearly proportional to the size of the household. The number of selected persons was: 1 person in households with 1 or 2 eligible persons; 2 persons if 3 or 4 eligible persons; 3 persons if 5 or 6 eligible persons; 4 persons if at least 7 eligible persons. To carry out this random selection in a simple way without equipment, interviewers used the next-birthday method.
We chose to select several people per dwelling on the recommendation of the local mediators in order to facilitate acceptance by the population. Indeed, selecting only one person could have been badly perceived in the households. We also wanted to have a sufficiently large sample in each neighbourhood.
Design effects were included by weighting data with the inverse of the probability of selection in each sampling unit.

We have changed the sentence on sampling method within households by:
“In a second step, we randomly selected at least one person in each household using the next-birthday method (ref). The number of selected persons was predetermined according to the number of eligible persons in the household: one if 2-3 eligible persons, two if 3-4 persons, three if 5-6 persons and four if 7 or over persons”

We have also added the following reference for the next-birthday method:
Salmon CT, Nichols JS. The Next-Birthday Method of Respondent Selection. Public Opinion Quarterly 1983;47(2):270-76. doi: https://doi.org/10.1086/268785

*Given that household could be considered the unit of analysis within the neighborhoods and the finding of cases within households being a significant risk it would appear that analysis at the household level may be more appropriate. I defer to the statistical reviewer on this, but I would ideally like to see some input for spatial effects. The clustering of certain characteristics such as young age (families with children) and obesity within infected households could explain some of the associations seen.

We had initially considered testing a multilevel model including variables at the individual level and at the household level (housing characteristics and household structure). However, the study design did not allow this analysis:
- Due to a time lag between the epidemic period and the survey period, some people indicated in the questionnaire that they were living in another dwelling in the neighbourhood during the lockdown. For these people, it was not possible to identify whether they lived with other survey participants. In addition, people from the same household sometimes gave different responses since the household/dwelling questions were asked in the individual questionnaire.
- The average number of people included per household is low (1.7) due to the sampling of individuals and the participation rate. Therefore, the results of a multilevel model would be not very different from the multivariate model performed. This type of analysis would have been more relevant if we had tested all people in each household.
For these reasons, all variables were explored at the individual level, including household characteristics. The variable "clinical cases of Covid-19 in the household" does not correspond to seropositive people in a household but to the reported number of persons with clinical signs of Covid-

19 or who consulted for suspected Covid-19 during the epidemic wave. We also collected information on household structure in the questionnaire (number of people aged under 12, 12-17 or 18 or over) and we tested "at least one child in the household" and "at least one child under 12 in the household" with seropositivity. These two variables were not significant. For obesity, analysis within a household would indeed be interesting but we measured BMI only among the participants.
We have added the following note below the tables to define “Clinical COVID-19 cases in the household” variable:
“Clinical COVID-19 cases in the household: Number of people, except the respondent, with clinical signs of covid-19 (cough, fever), a positive RT-PCR test or who were consulted for suspected covid-19 since 24 February 2020”

We have also added “At least one child in the household” variable to Table 1.

We have added a limit to the discussion section:
“A more in-depth analysis at the household level would be relevant in view of intra-household infections. However, our study design did not allow for this type of analysis.”

*Need clearer explanation of what is included in multivariable analysis, is it just age, sex and neighbourhood? If so why only these three variable? Report age as strongly related to seropositivity but important to know whether this was explained by multigenerational households, where people >65 living in the same household as those in the higher risk groups 15-64?
The multivariate analysis does not only include these three variables, but all the variables described in Table 2. The sentence "A forward selection procedure was applied with age, sex and neighbourhood being forced into the model" means that these three variables were compulsorily included in the model regardless of their p values when the forward selection procedure was performed.
We have reworded this paragraph as:
“Age, sex and neighbourhood were always retained into the multivariable model. For the other variables, a forward selection procedure was applied and variables with a p-value <0.1 were retained. Interactions were tested.”

For people aged 65, we did not collect the age of all the people in the households (only the number of people aged under 12, 12-17 or 18 or over). Our analyses indicated lower odds for people aged 65 years and over regardless of the number of people in the dwellings, but it is difficult to further investigate this issue with the data collected. However, the qualitative study carried out in a second phase (not yet published in English language but available in a French report : https://creaiors-occitanie.fr/wp-content/uploads/2021/07/CREAI-ORS-Occitanie-Les-Gitans-de-Perpignan-face-a-la-COVID-19-Analyse-dun-cluster-hypotheses-Rapport-final.pdf) provided important information on the reasons why such a low level of infection was found among people aged 65 years or over, which we explained in the discussion. The high risk for people aged 65 or over was quickly assimilated by the population. In consequence, these older people deliberately isolated themselves and were protected by the other people in the community.

Minor comments
Abstract:

*I am unsure if Gypsy community is the preferred self-designation of these communities but defer to the authors to select the most appropriate term. In several of the cited publications they are referred to Roma communities.

We have changed “Gypsy” by “Roma” in the text. Nevertheless, this community does not recognise itself in the generic term "Roma", but they call themselves "gitan" in French or "gitano" in Catalan.

Therefore, we have added “Roma communities, calling themselves “gitans” (gypsies)” in the Introduction.

*Page 3, line 11, change contamination to prior infection.
We have made the change in the ‘abstract’ statement and in the ‘introduction’ statement

Introduction:
*Page 5, line 14 needs a reference

This was a mistake. We have added the following references:
• Bambra C, Riordan R, Ford J, et al. The COVID-19 pandemic and health inequalities. J Epidemiol Community Health 2020;74(11):964-68. doi: 10.1136/jech-2020-214401
• DREES. Les inégalités sociales face à l'épidémie de Covid-19. Etat des lieux et perspectives [in French]. Les dossiers de la DREES, 2020:40.
• Wright L, Steptoe A, Fancourt D. Are we all in this together? Longitudinal assessment of cumulative adversities by socioeconomic position in the first 3 weeks of lockdown in the UK. J Epidemiol Community Health 2020;74(9):683-88. doi: 10.1136/jech-2020-214475 [published Online First: 2020/06/07]
• Gonzalez-Rabago Y, Cabezas-Rodriguez A, Martin U. Social Inequalities in Health Determinants in Spanish Children during the COVID-19 Lockdown. Int J Environ Res Public Health 2021;18(8) doi: 10.3390/ijerph18084087 [published Online First: 2021/05/01]

*line 20, in all of France to in France
We have made the change
*line 23, having work to being employed or in work
We have made the change

*line 32, The discussion on health understanding references an article which is a bit more nuanced than mentioned here (from the referenced articles (ref. 7) discussion "On the other hand, sickness is what “is seen”—a negative aspect of their personal and social life—and this is generally translated into a state of denial up to the limit. When the sickness is very severe and there are consequences, it is thus transformed into something tangible and visible, and one must therefore act.")

We have reworded the sentence by:
“They have their own perception of health and sickness. Sickness must have visible and tangible consequences for them to recognise it and act accordingly”

*Page 6 line 48-52, awkward wording around mentally able to participate, if individuals had to give informed consent then that would surely be the required mental criteria to attend the study location and so whether someone was physically able to attend the study site would be the inly true requirement at this stage.

We excluded people who were not able to answer a questionnaire when we selected people in the households. Consent from the selected persons was sought at the second stage when they visited a covid centre. Eligibility and consent are therefore two independent stages.

We propose to delete the word "mentally" but to keep “able to answer the survey questionnaire.”

*Univariate and multivariate should be changed to univariable and multivariable throughout as the authors are referring to the number of variables in the analysis of a single outcome measure

(serological status).

We have changed the two terms

*Page 7, line 25-26, sentence doesn;t seem to fit in the paragraph, rework.

The word "were" was missing, but we have deleted the sentence since it was redundant with the following sentences.

*Page 7, line 37-40, change to "Samples were stored locally for a maximum of 12 hours at less than 5degrees before being transferred to the laboratory at Perpignan hospital."

We have changed the sentence to your proposal.

*Page 9 line 10-12, as the seroprevalence was much higher in A than B and C it may be useful to provide a descriptive table of participant characteristics for the subsequent variables stratified by neighborhood.

We have made this table, but in order not to overload the article we propose to add it as supplementary material (see: Supplementary table S1). The most important differences per neighbourhood concern housing and are described in the Study Population paragraph.

*Page 9 line 52-53, less likely to be seropositive to have reduced odds of being seropositive, and change throughout as you are reporting odds ratios.

We have changed the paragraphs as suggested.

*Page 14 line 11-14. It does not seem reasonably to compare the prevalence in an urban population in Perpignan to a generally more rural region, it would be preferable to compare to general Perpignan prevalence if available and if not perhaps for other French cities of similar size/density.

Unfortunately, we have no data on the prevalence of Covid-19 in Perpignan or in other French cities during the first epidemic wave. Only hospitalisation data allowed us to observe the evolution of the epidemic in the cities. Very few RT-PCR tests were performed at the time and only the seroprevalence study referenced in the article provided an estimate at national and regional scales. Furthermore, it does not seem appropriate to compare these results with a geographical area far from Perpignan because, at the time of the first lockdown, the viral circulation was very heterogeneous (with a circulation mainly in the east of the country). However, a study of the Perpignan hospital (mentioned in the Introduction) supports the hypothesis of low circulation of the virus in the rest of Perpignan. Indeed, before our study, the Hospital made a map of the places of residence of the hospitalised people, and it revealed a strong concentration of hospitalised people in the three targeted neighbourhoods. The origin of the epidemic in these neighbourhoods may have been an evangelical congregation in Eastern France (Mulhouse) in February 2020. After the first reported cases, the epidemic did not spread much in the rest of the city of Perpignan probably because of the limited contacts of the gypsy population outside the neighbourhoods and the lockdown in March.

*Page 14 line 22-24. The authors have not investigate the temporal association between aguesia/anosmia and infection. It is therefore not possible from these results to reference this as an early warning symptom or one that could trigger self-isolation.

Indeed, we did not study temporality in our study, we have clarified the paragraph:

“The specificity of ageusia/anosmia symptoms was found very high, although this could not be confirmed by a temporal analysis which was not possible in this cross-sectional study. Such a high specificity has already been observed in numerous other studies. It would be useful for developing a strategy for early diagnosis of COVID-19 and self-isolation.”

*Page 15 line 5-8. The authors discuss the finding of lower prevalence in those that were working outside the home everyday. I agree that this is an interesting finding but without context it is difficult to question the causes of this. What were the types of work people were doing, were they high risk professions (healthcare, meatpacking, service industry) or lower risk professions (ones spending a lot of time outside)? Again this finding may be explained by not taking into account the household component of the design if generally more individuals were enrolled from households where no-one worked compare to the number of individuals enrolled from households where people worked during the lockdown.

We agree that it is difficult to interpret this association. We unfortunately did not collect information on the type of work, and we also could not collect precise information on the socio-economic status of the participants, as explained in the methods. Therefore, we could only hypothesise that this finding might be explained by differences in socio-economic status. Indeed, the average socio-economic status of the study population was very low, most inhabitants were living thanks to social benefits, and we observed during the field study that those who were working apparently had more income and higher socio-economic status than those unemployed, but this could not be quantified. Because dwellings were selected by systematic sampling, dwellings with workers had the same probability to be selected than dwellings without workers, thus we don’t think that results were biased by the sampling design.

We have kept the hypothesis on socio-economic status, but we have modified the second hypothesis: “Our study also confirms findings elsewhere that the risk of transmission is greater when a clinical case is present in the same household21 22. Working outside the home during the first lockdown was associated with a lower risk of seropositivity. This result may reflect a higher socioeconomic status of people who worked. Other hypotheses (compliance with barriers measures, healthy worker effect…) could be formulated to explain this result, but cannot be further explored without additional data”

*Overall I think this is important data highlighting the difficulty that public health bodies/hospitals can face in understanding infectious disease epidemiology in marginalised populations and would be a good fit for BMJ open, however, some changes are required and the manuscript would benefit from further improvements to it's style in English.

Thank you for your general assessment. We regret that the style was not satisfactory, the article had been revised by a mother-tongue English-speaking copyeditor. We hope that the revisions made will be more appropriate.

VERSION 2 – REVIEW

REVIEWER	Mitchell, Hannah Queen's University Belfast
REVIEW RETURNED	26-Oct-2021

GENERAL COMMENTS	I thank the authors for responding to my comments in full. There are just some grammatical errors which need corrected. Page 7 line 25- Then, they implemented... specify who they are, Page 8 line 30- Detailed characteristics by neighbourhood are...

	Page 13 lines 25/26... was found to be very high Page 14 line 14 (compliance with barriers measures, health worker effect....) either state all or put in etc not ...

REVIEWER	Simons, David University of London
REVIEW RETURNED	06-Oct-2021

GENERAL COMMENTS	The authors have responded comprehensively to comments made by the editor and two reviewers, which is particularly helpful given the open review process. The writing style has improved in this revision and is well structured. The authors have addressed my primary concerns and expanded on the limitations to their study design and drawing inference from their findings. I have no further major concerns, there are some minor typographic mistakes but these will likely be picked up at the proof stage. I commend this manuscript for publication. Well done on this important piece of public health research.