Dear Dr. Pollán,

Thank you for sending us your paper. We sent it for external peer review and discussed it at our manuscript committee meeting. We recognise its potential importance and relevance to general medical readers, but I am afraid that we have not yet been able to reach a final decision on it because several important aspects of the work still need clarifying.

We hope very much that you will be willing and able to revise your paper as explained below in the report from the manuscript meeting, so that we will be in a better position to understand your study and decide whether the BMJ is the right journal for it. We are looking forward to reading the revised version and, we hope, reaching a decision.

Please remember that the author list and order were finalised upon initial submission, and reviewers and editors judged the paper in light of this information, particularly regarding any competing interests. If authors are later added to a paper this process is subverted. In that case, we reserve the right to rescind any previous decision or return the paper to the review process. Please also remember that we reserve the right to require formation of an authorship group when there are a large number of authors.

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Associate Editor
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**Report from The BMJ’s manuscript committee meeting**

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

Members of the committee were: Elizabeth Loder (chair), Julie Morris (statistician), David Ludwig, Tiago Villanueva, Joe Ross, John Fletcher

Decision: Put points

Detailed comments from the meeting:

First, please revise your paper to respond to all of the comments by the reviewers. Their reports are available at the end of this letter, below.
Please also respond to these additional comments by the committee:

- Statistical comments:
  In general, the methodology and the statistical analysis used appears appropriate. However, there are a few issues relating to the serosurvey and the estimates of institutional deaths which should be addressed:

  1. It would be useful to include more details of the serosurvey in the text, rather than simply referring to the Lancet paper (Reference 6 - which covers the period April 27 to May 11, whereas this study uses data from an extended period April 27 to June 22). For example, the response rate of the survey should be given as well as the number of non-valid results.

  2. A sensitivity analysis which corrects for the estimated sensitivity and specificity of the antibody detection test is carried out, using point estimates derived from a meta-analysis of diagnostic accuracy studies, and appropriately incorporates the associated variance of the estimates. Although full details are provided in the Supplementary material, it would be helpful to expand a description of this sensitivity/specificity information in the text to include the range of sensitivity/specificity values obtained from these studies.

  3. An estimate of the number of institutional deaths (which are then subtracted from all deaths) is derived from a variety of Regional sources (Supplementary Table 1). How accurate are these figures? It is slightly concerning that the confirmed to suspected COVID-19 death ratios are very different between regions (eg. Andalucia records 558 confirmed and 0 suspected COVID-19 deaths in nursing homes, whereas Madrid records 1,253 confirmed and 4,734 suspected COVID-19 deaths in nursing homes). Is it possible that for some regions the number of confirmed plus suspected COVID-19 death reported is a gross underestimate? How much do the IFR estimates vary between regions?

Editor's comments:

- Please report the response rate for the serosurvey. That is what proportion of households approached consented to take part and provided samples?

- Please report the results of the serosurvey in a little more detail. What were the proportions of positive, negative and indeterminate results for each age and were there any missing data?

- Please explain and discuss the large differences in the ratio of confirmed vs suspected COVID deaths between regions reported in Supplementary Table 1.

In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how you have dealt with them in the paper.

Comments from Reviewers

Reviewer: 1

Recommendation:

Comments:
The authors provide a comprehensive and concise overview of the infection fatality risk of SARS-CoV-2 in their nation's population. The article is well constructed and experimental methodologies well conducted, analysed and explained. There are a few grammatical errors that can be improved prior to publication.

Additional Questions:
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Reviewer: 2

Recommendation:

Comments:
Many thanks to the authors for this very interesting piece of work covering a large study. The language used in the discussion is clear and approachable, making it accessible patients and carers with an interest in the subject matter. The paper is relatively clear in presenting the results of the research findings, the limitations of the review and suggestions for further research. However it does pose questions around the IFR rates for different population groups other than age and gender which are not part of the analysis. Conclusions could be more rounded on the continued need for control measures.

Are the questions the paper addresses relevant and important to patients and/or carers?

The topic is very relevant and pertinent to patients and carers. Anxiety around being infected with COVID-19, especially for patients with underlying health conditions is high as local outbreaks continue and the infection rate increases. This study, which takes place exclusively in non-institutional settings provides a vital aspect on the academic response to COVID-19. It will offer important messages for older groups who may also have underlying conditions who are out and about in the community or those caring for them and could help their decision making about their choices as a second wave looks likely. It could also be used in the public debate around how we can best live with COVID-19 and maintain economic viability.

The section on P3 'What is already known about this topic' is useful in setting the scene for the study. The paper clearly describes its additionality to the body of research on the risk of COVID-19 in 'What this study adds'. The Introduction on P4 is clear and offers the context and rationale for the study and the intention of the study to use excess mortality as a research tool to complement the IFR and the reason for doing this.

The data estimating excess deaths is of particular relevance to patients and carers. The indirect deaths and ill health have been alluded to since the pandemic began. P8 offers some explanation of the morbidity due to the rationing of services we have seen during the Pandemic, which patients and carers will be able to relate to and which is very useful.

The need the study identified for further and specific work in care homes was welcome as comparing IFR in the community and in institutional settings would be very helpful to patients and carers.

The Table on P18 was very helpful in understanding the narrative and comparing the IFR for the different age/gender groups. Whilst it is widely reported that older groups and males are more susceptible to mortality with COVID-19, i.e. this isn't in itself new, the data it provided on specific age groups and the rate of overall risk compared with seasonal flu was very useful.

Are there topics or issues that are missing, or need to be highlighted more?
The research topic took a binary approach and focused on infection rates and death rates, by age and gender, in order to obtain the Infection Fatality Risk (IFR). For me, there were unanswered questions about the study participants. It would have been interesting to see some disaggregation on:

- Any differences between urban and rural areas of IFR
- Occupational breakdown of IFR

The paper also made me want to know more about:

- Behavioural differences between age groups and genders helping to drive these different IFR levels?
  E.g. the level of adherence to government restrictions or their ability to adhere to restrictions?
- Any socio-economic drivers influencing the IFR rate?
- The role of PPE in the community to manage the IFR among vulnerable groups
- The impact of asymptomatic COVID-19 in the community and the IFR.
- Non-mortality aspects of COVID, such as 'long COVID'

Are the outcomes described/measured in the study important to patients and carers? Are there others that should have been considered?

The paper highlights the dilemmas faced by countries that have ageing populations. The methodology was explained at length, however, I still found it a little difficult to understand how data sets were utilized to reach the numbers cited. This was mitigated to some extent when the paper stated that findings were in-keeping with other studies.

There is a growing feeling among some in our communities to eschew the COVID-19 precautions, after months of social and economic disruption, which could ultimately affect the acuity of any second wave. This paper reminds us of the magnitude of risk that older/male groups face, which could support patients and carers in their conversations with their doctors about their treatment plans and their risk appetite from patients and from health providers around this – so support realistic medicine conversations.

Similarly, it may offer grist to the mill for sceptics and the majority of adults who’s IFR is relatively low. Therefore, possibly the outcomes could have attended more to the complexity of the virus and how it uses human behaviour to reach more vulnerable groups.

Do you have any suggestions that might help the author(s) strengthen their paper and make it more useful for doctors to share and discuss with patients/carers?

I had to read the paper a number of times before I felt I understood the study and its outcomes. Perhaps more plain English in the Results section on P2 would be helpful, with the data presented in a small table. Although I understand the statistical notation is the norm for research papers, lay people may not understand the significance – or otherwise of the percentages, hence my suggestion for a textual summary followed by a table with the numbers cited in this section.

The paper introduces the study by reminding us about the debate over the need and usefulness of lockdowns and social restrictions on P4. In the conclusion on Page 10, the authors consider that the evidence does “provide support for strong control measures”. I think it would have been useful here to make more of this at the conclusion – as it provides resolution to the research hypothesis. COVID-19 is after all, ten times the risk of seasonal flu (a fact that could usefully be made clear in the Results section on P2) – and enable patients and carers to see the evidenced for continued caution.

Do you think the level of patient/carer involvement in the study could have been improved? If there was none do you have ideas on how they might have done so?

There was no participant involvement in this study as it was using existing datasets and not embarking on any primary research. The write up of the study is relatively clear and approachable, but also technical in places, particularly in the results section for those without a statistical background to understand, which possibly some patient/carer involvement may have influenced to better explain the
statistical notations in accessible terms and conveyed the results in ways which were more meaningful for non-researchers.

Many thanks to the authors for this study.

Additional Questions:
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Reviewer: 3

Recommendation:

Comments:
This is an important and interesting paper utilising large-scale serological data from Spain as the basis for calculating the infection fatality risks. I have only specific points.

In the methods section on page 6 it says “Epidemiologic questionnaires and serology tests were administered to 68,292 individuals who participated in at least one round” this suggests some people participated in more than one round – could that be made clear.

Two categories of deaths – those with laboratory-confirmed COVID-19 and the estimated excess all-cause deaths were used. Detailed methods for calculating the latter are not provided, yet it is a key statistic. Reference to a study in Italy and reference to the EuroMOMO data for Spain are given, but not adequate information on estimation methods. Whilst it is reasonable to assume the two categories these are the lower and upper estimates, examining the historical series shows that several non-pandemic years have increases above the historical series for the ten prior years, so the excess could contain what would have been a non-pandemic “excess” component, and deaths with laboratory – confirmed COVID could have been deaths with, rather than from, the condition. Therefore there is some additional uncertainty (in both directions) that should be acknowledged. The fact that the excess mortality estimates are different to those given for Spain recently https://www.nature.com/articles/s41591-020-1112-0 (Kontis, V., et al. Magnitude, demographics and dynamics of the effect of the first wave of the COVID-19 pandemic on all-cause mortality in 21 industrialized countries. Nat Med (2020) when looking at the same period within the figures presented demonstrates this uncertainty.

There is clear evidence that some seropositive individuals become seronegative, and not just due to measurement error. This should be discussed.

The IFR reported relates to the age distribution of the population who became infected. It would be useful to see this adjusted to the age distribution of the total population, since this value is the one that was used in many of the initial projections which influenced the policy of countries with regard to the pandemic.
It is misleading to refer to COVID as having an IFR ten times larger than that for pandemic influenza. The authors cite the 2009 pandemic, known to be associated with either slightly lower or a little higher than usual seasonal flu mortality. They cannot generalise from this, and it would be very valuable if they would add a comparison with the IFR in previous pandemics, 1957-9, 1968-9, for which good data are available for Spain, and in particular to present these by age group.

Additional Questions:
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