PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	SARS-CoV-2 population-based seroprevalence studies in Europe: A scoping review
AUTHORS	Grant, Rebecca; Dub, Timothée; Andrianou, Xanthi; Nohynek, Hanna; Wilder-Smith, Annelies; Pezzotti, Patrizio; Fontanet, A

VERSION 1 – REVIEW

REVIEWER	Kamran Kadkhoda Cleveland Clinic, USA
REVIEW RETURNED	02-Oct-2020

GENERAL COMMENTS	This is a fair study and in fact we need more of these but by taking into account the pillars and necessities of sero-prevalence studies so the readership can educated as how such studies ought to be performed. Line 32: not a very accurate stamen. I disagree with making it sound like we already know the correlate of protection is antibody. It is sounder to say low sero-prevalence means low positive predictive value for antibody testing. However the variability stems from different study designs, local polices, and much more importantly different tests/kits and/or testing algorithms used. Not to mention >50% of articles used were not peer-reviewed so that's another bias. Line 33, the Spanish study is a good example of using one test for such conclusion without confirming the results with PRNT. Using a neutralization test is very important to avoid bias. On the other hand losing An several weeks after infection especially in asymptomatic and mild cases is well known now, further affecting the sero-prevalence estimates. Re line 42, please see: https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2020.25.30.2001374 Bottom-line is, if and only if we accept, antibody is the correlate of protection, to prevent large outbreaks and achieve herd immunity, we will need 75-80% of population sero-positive which clearly is not the case now and may never happen given public health preventive measures. This begs the question if sero-prevalence are really needed especially when vaccine becomes available. Which is the case with flu. I recommend including this into the manuscript.

REVIEWER	Maria Skaalum Petersen Department of Occupational Medicine and Public Health, the Faroese Hospital System & University of the Faroe Islands
REVIEW RETURNED	16-Jan-2021

GENERAL COMMENTS	The manuscript 'SARS-CoV-2 population-based seroprevalence studies in Europe: A scoping review' is highly relevant. The results from the seroprevalence studies are important e.g. for estimating the true prevalence of COVID 19 informing the public health officials. This manuscript is well-written and clear. There are few considerations that would benefit from more discussion, along with some comments/questions largely for clarification. In general, I suggest to add more references when referring to studies included. Specific comments: p4. L. 12. You write '….. capacity for testing are limited'. I suggest you add '…..are limited in most countries'. In the Faroe Islands and Iceland, testing capacity has not been an issues. p4, l. 34 You write '…..estimates of disease severity and….' Severity - is that the correct word? I get the impression it refers to severity of symptoms. I suggest rephrasing. P6, l.18. Why did you choose exactly 15 days before the end of the blood sample selection? Please explain. p.7, l.13, l14. Please add references to the studies when mentioned, e.g. from the general population (ref x-x), through household surveys (ref x-x) p7. L. 57, Six of the 12 studies, please include the reference to these studies. Reference 6 also reports estimate by age p8, l. 40. 'Three studies recruited…..'. Please include reference to the studies. p8, l- 50. 'Four general population studies…' Please include references to these studies. p9, l 37-40. You write: 'The studies among blood donors found seroprevalence to be largely lower than the seroprevalence in studies that used household surveys targeting the general population.' I find that this sentence too simplified. The prevalence among blood donors was comparable to some of the seroprevalence studies in the general population but lower than some, i.e. not in general lower as seen in table 1. I suggest rephrasing the sentence. p.10, l 3. 'A number of studies used the Euroimmun Elisa assay.' Please include reference to the studies p. 10, l. 9. 'Only three of the 23 studies used neuralization assays' . Please include references for the three studies p.11, l. 12. You write: 'Overwhelmed health-care systems not only disrupt the delivery of care to COVID- 19 patients, but also the delivery of non-COVID-19 health services.' I suggest including reference/es to support this statement- p. 11, l. 18. You write: 'Further, we now understand that transmission of SARS-CoV-2 is largely concentrated in crowded, close-contact.' Please add reference/s to support this statement. p. 11, l.35-36. Regarding the last sentence: 'As a result, we urgently need the development of effective vaccine candidates to deliver the required level of herd immunity in the population. regarding vaccine.'. This sentence seems outdated as the first vaccines are currently on the market and

	are being used. We can expect a vaccine shortage for some time to come. The vaccine shortage leads to longer time for an entire population to be vaccinated. Thus, there is a need for a strong effort to eliminate COVID-19 concurrent with rolling out vaccines. . I suggest rephrasing and nuance the last sentence.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Kamran Kadkhoda, Cleveland Clinic

Comments to the Author:
This is a fair study and in fact we need more of these but by taking into account the pillars and necessities of sero-prevalence studies so the readership can educated as how such studies ought to beperformed.
On behalf of my co-authors, I would like to thank Dr Kadkhoda for the insightful comments on our manuscript. We believe that our manuscript now highlights the limitation of currently not being able to comment on the persistence of antibodies or the correlates of protection, as well as the various paragraphs explaining sources of heterogeneity across the studies.
We have responded to the specific comments below.

Line 32: not a very accurate stamen. I disagree with making it sound like we already know the correlate of protection is antibody. It is sounder to say low sero-prevalence means low positive predictive value for antibody testing. However the variability stems from different study designs, local polices, and much more importantly different tests/kits and/or testing algorithms used. Not to mention >50% of articles used were not peer-reviewed so that's another bias.
The sentence has been revised as suggested and now reads:
All assays report high specificity as shown in Table 1, however, a context of low seroprevalence, it may still mean low positive predictive value for antibody testing.

Line 33, the Spanish study is a good example of using one test for such conclusion without confirming the results with PRNT. Using a neutralization test is very important to avoid bias. On the other hand losing An several weeks after infection especially in asymptomatic and mild cases is well known now, further affecting the sero-prevalence estimates.
Thank you for this comment. We believe we have highlighted these points in the fourth and fifth paragraphs of the Discussion. It is true indeed, that antibody waning may take place after several weeks.

Re line 42, please see:
https://urldefense.com/v3/__https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2020.25.30.2001374__;!!JFdNOqOXpB6UZW0!6oirt9ORR1_d0-ukFlPlJilO96cpIrkUJE4ymPlFPSH2ZJIYBfYYlDkfXjwyHyqc0m29ew$

Bottom-line is, if and only if we accept, antibody is the correlate of protection, to prevent large outbreaks and achieve herd immunity, we will need 75-80% of population sero-positive which clearly is not the case now and may never happen given public health preventive measures. This begs the question if sero-prevalence are really needed especially when vaccine becomes available. Which is the case with flu. I recommend including this into the manuscript.

Many thanks for sharing this interesting correspondence published in Eurosurveillance. We have included it in the references and now refer to it on several occasions in the Discussion.

Reviewer: 2
Dr. Maria Petersen, The Faroese Hospital System, University of the Faroe Islands

Comments to the Author:
The manuscript 'SARS-CoV-2 population-based seroprevalence studies in Europe: A scoping review' is highly relevant. The results from the seroprevalence studies are important e.g. for estimating the true prevalence of COVID 19 informing the public health officials. This manuscript is well-written and clear. There are few considerations that would benefit from more discussion, along with some comments/questions largely for clarification. In general, I suggest to add more references when referring to studies included.
On behalf of my co-authors, I would like to thank the reviewer for the thorough review of our manuscript. We have responded to each of the specific comments below:

Specific comments:
p4. L. 12. You write '….. capacity for testing are limited'. I suggest you add '…..are limited in most countries'. In the Faroe Islands and Iceland, testing capacity has not been an issues.
The manuscript has been revised to reflect that capacity for testing was limited in many countries across Europe in the initial stages of the first epidemic peak:
This is further exacerbated when availability of molecular tests for diagnosis of acute infection or capacity for testing are limited. This may have been the case in the initial stages of the first epidemic peak of COVID-19 in many countries across Europe.

p4, l. 34 You write '…..estimates of disease severity and….' Severity - is that the correct word? I get the impression it refers to severity of symptoms. I suggest rephrasing.
The manuscript has been revised for clarity and now reads:
early estimates of the extent of infection in the population often struggle to account for mild or asymptomatic infections that do not require medical care.

P6, l.18. Why did you choose exactly 15 days before the end of the blood sample selection? Please explain.
An explanation and a reference as to why 15 days was chosen has been added to the manuscript:
and compared them to the number of reported infections 15 days before the end of the blood sample collection period for the seroprevalence study, based on current understanding of anti-SARS-CoV-2 antibody kinetics and the ability to detect these antibodies in the second week of infection.

p.7, l.13, l14. Please add references to the studies when mentioned, e.g. from the general population (ref x-x), through household surveys (ref x-x)
The references have been added in as requested.

p7. L. 57, Six of the 12 studies, please include the reference to these studies. Reference 6 also reports estimate by age
The references have been added in to the end of the sentence, in addition to the reference to the study from Faroe Islands.

p8, l. 40. 'Three studies recruited…..'. Please include reference to the studies.
The references have been added in as requested.

p8, l- 50. 'Four general population studies…' Please include references to these studies.
The references have been added in as requested.

p9, l 37-40. You write: 'The studies among blood donors found seroprevalence to be largely lower than the seroprevalence in studies that used household surveys targeting the general population.' I find that this sentence too simplified. The prevalence among blood donors was comparable to some of the seroprevalence studies in the general population but lower than some, i.e. not in general lower as seen in table 1. I suggest rephrasing the sentence.
The sentence has been revised as suggested and now reads:
The studies among blood donors found seroprevalence to be largely comparable to studies that used household surveys targeting the general population, as shown in Table 1, with the exception of the blood donors in Lombardy.

p.10, l 3. 'A number of studies used the Euroimmun Elisa assay.' Please include reference to the studies
The references have been added in as requested.

p. 10, l. 9. 'Only three of the 23 studies used neutralization assays' . Please include references for the three studies
The references have been added in as requested.

p.11, l. 12. You write: 'Overwhelmed health-care systems not only disrupt the delivery of care to COVID-19 patients, but also the delivery of non-COVID-19 health services.' I suggest including reference/es to support this statement-
An additional reference has been included to support this statement.

p. 11, l. 18. You write: 'Further, we now understand that transmission of SARS-CoV-2 is largely concentrated in crowded, close-contact.' Please add reference/s to support this statement.
The sentence has been rephrased and a reference has been added to support the rephrased statement:
Further, we now understand that transmission of SARS-CoV-2 is largely concentrated in close-contact settings through large droplets, aerosols and contaminated surfaces.

p. 11, l.35-36. Regarding the last sentence: 'As a result, we urgently need the development of effective vaccine candidates to deliver the required level of herd immunity in the population. regarding vaccine.'. This sentence seems outdated as the first vaccines are currently on the market and are being used. We can expect a vaccine shortage for some time to come. The vaccine shortage leads to longer time for an entire population to be vaccinated. Thus, there is a need for a strong effort to eliminate COVID-19 concurrent with rolling out vaccines. . I suggest rephrasing and nuance the last sentence.
The sentence has been revised since it was first written to reflect the situation in August/September 2020. It now reads:
In parallel, efficient rollout of effective vaccines is needed to deliver the required level of herd immunity in the population.

VERSION 2 – REVIEW

REVIEWER	Maria Skaalum Petersen Department of Occupational Medicine and Public Health, the Faroese Hospital System & Centre of Health Science, University of the Faroe Islands
REVIEW RETURNED	25-Feb-2021

GENERAL COMMENTS	My comments and concerns have been addressed satisfactorily.