

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	A systematic review of seroprevalence of SARS-CoV-2 antibodies and appraisal of evidence, prior to the widespread introduction of vaccine programmes in the WHO European Region, January - December 2020
AUTHORS	Vaughan, Aisling ; Duffell, Erika; Freidl, Gudrun; Lemos, Diogo; Nardone, Anthony; Valenciano, M; Subissi, Lorenzo; Bergeri, Isabel; Broberg, Eeva; Penttinen, Pasi; Pebody, Richard; Keramarou, Maria

VERSION 1 – REVIEW

REVIEWER	Ratnatunga, Champa University of Peradeniya, Microbiology
REVIEW RETURNED	25-Nov-2022

GENERAL COMMENTS	A comprehensive review, that is well presented and shows the variation in seroprevalence across nations and regions over the pre-vaccination era. Categorizing data into national/ subnational/ regional/ as well as by type of sampling adds depth of interpretation and provides essential insight into the dynamics of disease spread. An insightful and excellent piece of work. My only suggestion would be to perhaps add a simplified figure which shows what areas/ countries/ populations had low seroprevalence and which had high seroprevalence perhaps including morbidity and mortality stats in the same, and state the known and potential risk factors/ protective factors in those subsets. This would clearly highlight the areas in need of urgent public health intervention in a subsequent respiratory infection as well as priority areas of vaccination.
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REVIEWER	Malijan, Greco Mark University of the Philippines Manila National Institutes of Health, Institute of Herbal Medicine
REVIEW RETURNED	29-Nov-2022

GENERAL COMMENTS	<p>Thank you for this important work. I have added comments and suggestions to help improve the clarity of the paper.</p> <p>Introduction: * Rather than introducing how SARS-CoV-2 started in 2019 and the burden of pandemic in March 2022, it may be better to focus the introduction on the how seroprevalence estimates have been used and applied during COVID-19 and what can we potentially learn from them for future pandemic preparedness. * Global SARS-CoV-2 seroprevalence in 2020 was estimated in this paper:</p>
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<https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0252617>. To contextualise existing literature, it may be worth noting some limitations from this earlier work pertinent to the WHO European Region (and member states) and how the current work may be positioned in relation to those issues.

Methods:

pg.3, line 39

* To avoid confusion for the readers, please clarify the dates by spelling out the month (e.g. 21 October 2020 and 12 January 2021). Was an additional search of the databases performed as the review was reaching completion?

pg.4, lines 27-40

* Was the quality assessment scoring system validated? If yes, how?

* Why was it deemed necessary to develop a new quality assessment scoring system? How does this compare to existing ROB scoring systems?

* How was the quality assessment performed? Was it performed by at least two reviewers? If yes, how were disagreements adjudicated and what score difference was considered large enough to be “disagreement”?

pg.4, lines 49-55 and pg. 5, lines 3-8

* Please describe in greater detail how data analysis was performed.

What “descriptive statistics” were used and in what kind of data?

* It may be meaningful to estimate the seroprevalence in the region and in subpopulations/timing of interest, especially because the general objective aims “to measure pre-existing and cumulative seropositivity”. However, it is appropriate not to include pooled estimates if there is expected significant heterogeneity which may affect interpretation of results. In such case, please be explicit in explaining the rationale to the readers.

* When exploring “variations according to specific characteristics”, what were the subgroups of interests and how were they selected?

Supplementary methods: S1.2 search terms

* Please include the constraints used, if any, to identify studies coming from the WHO European Region member states.

Results:

* The results section will benefit from some re-structuring to improve cohesion. I suggest using subheadings to guide the reader and to present the results according to the main analyses framework.

Figure 1

* Why are there two separate boxes for the search done for 1/1/2020-20/10/2020 and 21/10/2020-31/12/2020?

* It will be more replicable/transparent to include the output for each database.

* Please clarify what the other sources were.

pg.16

* In the narrative, please better clarify whether the sample sizes (n=) that are mentioned pertain to studies or to the population included in specific studies.

pg.17

* High-risk groups were part of the exclusion criteria. Why were patients with malignant conditions and those requiring hemodialysis, even if they were seeking care for non-COVID-19 reasons, not considered potentially high risk?

pg.18, lines 37-46

* Why are there discrepancies in the correlation coefficients presented in the text and in the figures?

	<p>Discussion: pg.18, lines 50-56 * To limit confusion, please revise the statements to avoid use of terms that have specific meaning in statistics if these were not explicitly explored in the analyses. pg.19, lines 3-14 * Early 2020 and later (“throughout”) 2020 were mentioned, but these were not explicitly defined in the previous sections. While there are supplementary figures at the country level showing seroprevalence levels in relation to the number of new cases and cumulative cases, it remains unclear how pre-community transmission/during community transmission (early 2020/late 2020) were defined and used. Some additional questions in the discussion that the authors may wish to explore to help improve the study’s impact: * How can the results of the study inform current pandemic efforts at various levels? * How can the results from the study inform future pandemic preparedness?</p> <p>Conclusion: * I suggest to temper the conclusion based on the working understanding that seroprevalence/antibody level is not the only predictor of susceptibility to infection.</p>
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REVIEWER	Fakhri, Moloud Mazandaran University of Medical Sciences
REVIEW RETURNED	01-Mar-2023

GENERAL COMMENTS	Major Revision
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1 (Dr. Champa Ratnatunga, University of Peradeniya)

Comments to the Author:

A comprehensive review, that is well presented and shows the variation in seroprevalence across nations and regions over the pre-vaccination era. Categorizing data into national/ subnational/ regional/ as well as by type of sampling adds depth of interpretation and provides essential insight into the dynamics of disease spread. An insightful and excellent piece of work.

Author response: Dear Dr. Champa Ratnatunga, thank you for your kind words regarding this manuscript.

My only suggestion would be to perhaps add a simplified figure which shows what areas/ countries/ populations had low seroprevalence and which had high seroprevalence perhaps including morbidity and mortality stats in the same, and state the known and potential risk factors/ protective factors in those subsets. This would clearly highlight the areas in need of urgent public health intervention in a subsequent respiratory infection as well as priority areas of vaccination.

Author response: We have provided figures in the supplementary files to indicate seroprevalence over time, by country and subgroup. These provide a clear overview of prevalence across the different geographical areas/populations and this information can be reviewed alongside the

correlation analyses that we undertook between cumulative incidence and deaths and the seroprevalence estimates from the general population.

Reviewer: 2 (Dr. Greco Mark Malijan, University of the Philippines Manila National Institutes of Health)

Comments to the Author:

Thank you for this important work. I have added comments and suggestions to help improve the clarity of the paper.

Author response: Dear Dr. Greco Mark Malijan, thank you for your kind review of this manuscript. We have provided answers to each of your comments below.

Introduction:

Comment 1: Rather than introducing how SARS-CoV-2 started in 2019 and the burden of pandemic in March 2022, it may be better to focus the introduction on the how seroprevalence estimates have been used and applied during COVID-19 and what can we potentially learn from them for future pandemic preparedness.

Author response: Thank you for this comment and suggestion to discuss the value of seroprevalence studies in the overall response to the COVID-19 pandemic and future pandemic preparedness. We have addressed this in the discussion and conclusion of the article.

Comment 2: Global SARS-CoV-2 seroprevalence in 2020 was estimated in this paper: <https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0252617>. To contextualise existing literature, it may be worth noting some limitations from this earlier work pertinent to the WHO European Region (and member states) and how the current work may be positioned in relation to those issues.

Author response: Thank you for highlighting this paper. We reference this study in the discussion and highlight the added value of this study in the section below:

“This systematic review comprehensively describes the seroprevalence of SARS-CoV-2 in the first year of the pandemic, prior to the widespread implementation of national vaccine programs. In addition, with the inclusion of as yet unpublished data from LMICs, this review contributes to research equity across Member States income levels and provides a more representative overview of the situation in the WHO European Region than would published studies alone. In addition, we evaluated the UNITY study alignment of studies to assess quality and comparability.”

Methods:

pg.3, line 39

Comment 3: To avoid confusion for the readers, please clarify the dates by spelling out the month (e.g. 21 October 2020 and 12 January 2021). Was an additional search of the databases performed as the review was reaching completion?

Author response:

The dates have now been spelled out as suggested. An additional and final search was conducted on 12 January 2021.

pg.4, lines 27-40

Comment 4: Was the quality assessment scoring system validated? If yes, how?

Author response:

The quality assessment scoring system was adapted from the Joana Briggs checklist for prevalence studies. We did not perform an independent validation of assessment scoring system in this study.

Comment 5: Why was it deemed necessary to develop a new quality assessment scoring system? How does this compare to existing ROB scoring systems?

Author response:

The quality assessment scoring system was adapted from the Joana Briggs checklist. The manuscript has now been amended to reflect this and the Joanna Briggs Institute working group have been referenced accordingly: <https://pubmed.ncbi.nlm.nih.gov/26317388/>

Comment 6: How was the quality assessment performed? Was it performed by at least two reviewers? If yes, how were disagreements adjudicated and what score difference was considered large enough to be “disagreement”?

Author response: Thank you for highlighting that this was not included. Two independent researchers conducted the bias assessment and any disagreement (in this case any difference in score) was evaluated by a third reviewer.

We have now added the following: “Two independent researchers conducted the quality assessment; a third researcher resolved any disagreements.”

pg.4, lines 49-55 and pg. 5, lines 3-8

Comment 7: Please describe in greater detail how data analysis was performed. What “descriptive statistics” were used and in what kind of data?

Author response: Now included

Comment 8: It may be meaningful to estimate the seroprevalence in the region and in subpopulations/timing of interest, especially because the general objective aims “to measure pre-existing and cumulative seropositivity”. However, it is appropriate not to include pooled estimates if there is expected significant heterogeneity which may affect interpretation of results. In such case, please be explicit in explaining the rationale to the readers.

Author response: We agree, and this is one of the limitations of this study that we have outlined. Given the degree of heterogeneity among the studies, comparability across studies would be difficult. In order allow for better comparability across studies and countries, there is a need for wider standardisation of seroprevalence study methodologies. We include an explanation in the following line in the discussion:

“Due to such heterogeneity, we opted to not provide one pooled estimate nor conduct a meta-analysis, as interpretation would be difficult and may not accurately reflect the picture in the WHO European Region.”

Comment 9: When exploring “variations according to specific characteristics”, what were the subgroups of interests and how were they selected?

Author response: We explored variations in seroprevalence over time, by geographic location and population type. This has now been further amended in the methods section, under Data analysis : “We used descriptive statistics to summarize results. We generated forest plots to display the data and explore variations according to specific characteristics, including time, geographic location and population group.”

Supplementary methods: S1.2 search terms

Comment 10: Please include the constraints used, if any, to identify studies coming from the WHO European Region member states.

Author response: This is outlined in Table S1 Inclusion and exclusion criteria

Results:

Comment 11: The results section will benefit from some re-structuring to improve cohesion. I suggest using subheadings to guide the reader and to present the results according to the main analyses framework.

Author response: Thank you for this suggestion. Subheadings have been added to the results section.

Figure 1

Comment 12: Why are there two separate boxes for the search done for 1/1/2020-20/10/2020 and 21/10/2020-31/12/2020?

Author response: This is to highlight the number of returns for each search, prior to deduplication.

Comment 13: It will be more replicable/transparent to include the output for each database. Please clarify what the other sources were.

Author response:

As the WHO COVID-19 literature database is compiled from many other databases including MEDLINE and Embase, then de-duplicated, breaking down by the various databases will not be significant as the citations could have had many homes before arriving to the unique citation within WHO COVID-19 Database. Please find information regarding the WHO “COVID-19 Global literature on coronavirus disease” database here: <https://search.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov/> . Please also find here a link to the description of the database, with a full link to the search here: https://www.who.int/docs/default-source/coronaviruse/who-covid-19-database/who-covid-19_sources_searchstrategy_20210105.pdf?sfvrsn=480292c0_9

pg.16

Comment 14: In the narrative, please better clarify whether the sample sizes (n=) that are mentioned pertain to studies or to the population included in specific studies.

Author response: These pertain to the estimates from the study, for example: “A total of 45 studies provided seroprevalence estimates (n=105) from community or household samples and 39 studies (87%) were found to be of high or medium quality.”

pg.17

Comment 15: High-risk groups were part of the exclusion criteria. Why were patients with malignant conditions and those requiring hemodialysis, even if they were seeking care for non-COVID-19 reasons, not considered potentially high risk?

Author response: For the purposes of this review, anyone seeking health-care for unrelated reasons were considered representative of the general population. High-risk in this case relates to increased risk of SARS-CoV-2 infection, and includes individuals such as healthcare workers.

pg.18, lines 37-46

Comment 16: Why are there discrepancies in the correlation coefficients presented in the text and in the figures?

Author response: Thank you for highlighting this. They have now been aligned.

Discussion:

pg.18, lines 50-56

Comment 17: To limit confusion, please revise the statements to avoid use of terms that have specific meaning in statistics if these were not explicitly explored in the analyses.

Author response: The manuscript has been amended accordingly:

“A large variation in study methodologies was noted across the studies, with an overrepresentation of studies from high-income countries in Western Europe.”.

pg.19, lines 3-14

Comment 18: Early 2020 and later (“throughout”) 2020 were mentioned, but these were not explicitly defined in the previous sections. While there are supplementary figures at the country level showing seroprevalence levels in relation to the number of new cases and cumulative cases, it remains unclear how pre-community transmission/during community transmission (early 2020/late 2020) were defined and used.

Author response: We used the WHO Definition of the categories for transmission pattern outlined in the WHO Global surveillance for COVID-19 caused by human infection with COVID-19 virus interim guidance here: <https://www.who.int/publications/i/item/who-2019-nCoV-surveillanceguidance-2020.7>

Some additional questions in the discussion that the authors may wish to explore to help improve the study's impact:

Comment 19: How can the results of the study inform current pandemic efforts at various levels?
How can the results from the study inform future pandemic preparedness?

Author response: The following line has been added to the Conclusion:

“Seroprevalence studies have been of great value to COVID-19 pandemic response efforts, providing estimates of the true extent and dynamics of SARS-CoV-2 infection overtime and the lessons identified from COVID-19, in particular the need for standardised global serosurveillance systems, will inform future pandemic preparedness.

Conclusion:

Comment 20: I suggest to temper the conclusion based on the working understanding that seroprevalence/antibody level is not the only predictor of susceptibility to infection.

Author response: We agree with this and have included a line in the discussion:

“In addition, while seroprevalence studies provide an estimate of population exposure, seropositivity is not the only predictor of susceptibility to infection. “

Reviewer: 3

Dr. Moloud Fakhri, Mazandaran University of Medical Sciences

Comments to the Author:

*** Please find comments from this reviewer in the attached file ***

Author response: Dear Dr. Moloud Fakhri, thank you for your review of our manuscript. We have taken your comments from the PDF file and answered them point-by-point below.

Comment 1: Why are other databases not searched? Scopus, web of sciences, cochrane

Author response: These resources are all captured by the WHO COVID-19 research database. Two scientific databases and one specialized resource is sufficient for a systematic review. There is also a publication that validated the comprehensiveness of the WHO COVID database here:
<https://www.sciencedirect.com/science/article/pii/S0895435622000671>

Comment 2: It seems that the article needs to be updated. Because now we are in the year 2023 and the covid 19 disease has new manifestations every day and many articles are published in this field.

Author response: This article focuses on the seroprevalence of SARS-CoV-2 antibodies prior to the roll out of vaccination programmes in the European Region. Another systematic review of studies undertaken during vaccination programmes can address questions related to infection-derived and antibody-derived antibodies and antibody kinetics overtime. This was beyond the scope of this review.

Comment 3: The study protocol should be registered on the PROSPERO web site

Author response: This question has been addressed above in the Editor section

Comment 4: Mention the Mesh keywords. Enter the search strategy for each site in this section

Author response: As the keywords in the search are lengthy, they have been included in the supplementary section under S1.2 Search terms

Comment 5: You have included only systematic review in the title of the study but in the text of the article, you have done a statistical analysis that shows a meta-analysis. Clear this confusion

Author response: We have not undertaken a true meta-analysis in the strictest sense (we have not undertaken any meta-analysis statistics to pool the) and outline the rationale behind this (i.e. the heterogeneity) in the limitations. We have now amended the title of the manuscript to: "A systematic review of seroprevalence of SARS-CoV-2 antibodies and appraisal of evidence, prior to the widespread introduction of vaccine programmes in the WHO European Region, January - December 2020"

Comment 6: Name the limitations of the study

Author response: The limitations of the study are described in full on Page 23 Line 3-24

Comment 7: 111 studies or 26.

Author response: 111 studies were included in this systematic review. 26 were excluded for the reasons listed in Figure 1.