PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Rate of asymptomatic COVID-19 among ascertained infections in different region and population groups in 2020: A systematic review and meta-analysis including 130,123 infections from 241 studies
AUTHORS	Chen, Xiao; Huang, Ziyue; Wang, Jingxuan; Zhao, Shi; Wong, Martin Chi-Sang; Chong, Ka; He, Daihai; Li, Jinhui

VERSION 1 – REVIEW

REVIEWER	Ivana Lapić University Hospital Centre Zagreb Department of Laboratory Diagnostics
REVIEW RETURNED	28-Mar-2021

GENERAL COMMENTS	The authors are to be congratulated on such a comprehensive analysis of published papers dealing with the asymptomatic rate of COVID-19 cases. There are only some minor issues that should be addressed before the paper would be suitable for publication: - Lines 93-100 - this part of the texts pertains more to the Materials and Methods section, and not Introduction - I suggest summarizing the data presented in the Supplementary table 1 in a few sentences or advantageously as a flowchart. In this form, it is hard to follow. - Paragraphs Literature screening and selection critera, and Data extraction and subgrouping schemes should be shortened, maybe by merging some sentences/points - The first paragraph of the Results section repeats what is already stated in Figure 1. Such repetition should be avoided. Please use one way or another to present your results.

REVIEWER	Jean-Paul Moatti Aix-Marseille Universite, IMERA
REVIEW RETURNED	13-Apr-2021

GENERAL COMMENTS	Determining the rate of asymptomatic infection is key for epidemiological modelling of COVID 19 dissemination and for informing public health management of the health crisis. Since estimations of such rate and its distribution according to patients characteristics has been quite heterogeneous through the numerous published studies, systematic review of the literature and quantitative meta-analysis are appropriate tools for providing appropriate estimates. Although some meta-analyses on this important topic have already been published, this one brings added value especially through the high number of included eligible studies. The process of identifying eligible studies and the use of the STATA "METAPROP" software are standard for such meta-analysis exercise but are implemented in a perfectly correct way.

	Minor revisions needed =
	The last sentence of the abstract should be suppressed since the paper indeed provides no results to determine cost-effective strategies of identifying and tracing 61 asymptomatic infections.
	The distinction between screening and non screening studies should be further clarified.
	Due to the limited number of studies involved in the case of children and pregnant women, limitations of the meta-analysis in these two groups should be mre emphasized in the Discussion section.
	The geographical heterogeneity of the estimated rates (with higher rates in European studies) should be further discussed (including the role of differences in health systems and access).

REVIEWER	Benjamin Bowe
	Saint Louis University, Epidemiology and Biostatistics
REVIEW RETURNED	13-Apr-2021

GENERAL COMMENTS	The rates of asymptomatic COVID-19 are important to know for public health officials, but something quite difficult to answer. While there are several reviews and meta-analyses on this subject, given possible spatiotemporal heterogeneity, and differences by other factors such as age, continued evaluation and investigation of population specific rates may be informative.
	I have a few comments for consideration:
	Given that the last study included here was published in July of last year, perhaps there might be an opportunity to update incorporated information to help derive estimates that are more current, considering the dynamicity of the pandemic, to enhance novelty.
	Along those lines, the authors note the limitations of using cross-sectional analyses. Updating the data might provide enough information to limit analyses to longitudinal studies. Alternatively, the authors might consider weighting by risk of bias.
	Generally, observational study participants will get tested for a reason; this is very likely to bias results (asymptomatic less likely to seek getting tested), and is not really discussed. Subgroup analysis by "screening" status uses a limited definition that could mean a lot of different things across the studies, so is not super clear the actual implication there.

REVIEWER	Linda Östlundh
	United Arab Emirates University College of Medicine and Health Sciences, National Medical Library
REVIEW RETURNED	24-Apr-2021

GENERAL COMMENTS	Below is a review of the methods part of the paper only. The peer review excludes the search strategies applied in the Chinese databases due to lack of language skills.
	The reporting of the search method of this review is very structured and follows the PRISMA guidelines. A copy of the search strategy applied in all databases is appended to the review and the authors have used a combination of MeSH terms and TextWords in the searches. However, a search technical enhancement of the search strategies is needed in order for the researcher to ensure that the search retrieves a result that ensure that the review is based on the best available evidence for this topic.
	Major suggestions:

116 Searching strategy

- Considering the rapid development of the research field of COVID-19, the fact that the result mainly includes studies from US and China and that the literature search for this review is conducted in July, 2020, I strongly suggest that the authors update the search.

- Please specify who of the authors conducted the search

- Information about the search strategy used including eventual filters or limitations (or the exclusion of such) applied for the search is needed.

- Please specify "highly relevant references". Are those the finally included papers? Who selected and conducted the screening of these reference lists?

Literature screening and selection criteria
- Please specify any software or reference management tool was used in the screening or if the screening was conducted by hand?

- Line 146: please specify if the "studies that analyzed the same group of subjects more than once" but with a larger population included, reports on the same measure / have the same research question?

463- References
- The reference to the PRISMA statement is to the PRISMA P (protocol) reporting guidelines. Please apply and refer to the PRISMA statement for Systematic Reviews and Meta-analysis instead.
Supplementary table 1: Search strategy for systematic review
- I would suggest the researchers to develop the inclusion of search-term variation in the "TextWord" search. This will enhance the search result and ensure that the best possible evidence is located. A tip is to have a look at the "entry terms" in PubMed's Mesh where additional search variations for "COVID-19" and "asymptomatic" is available. This will help the authors to a systematic search term inclusion.

- Phrasing of the keywords is missing (applies to most databases). By applying quotation marks ("Reported no symptom*") to the keywords that includes more than one search term, the specific term will be searched. A search without quotation marks generates a totally different and irrelevant result. A search on: Reported no symptom* in PubMed using the TextWord field generates 5,128 references (with no filter applied) while adding quotation marks retrieves 0 references. When phrasing is left out, the database translates the request automatically which mostly results in an irrelevant translation. The PubMed translation for the example below is as follows:

Search: Reported no symptom*[Text Word]
("reportable"[All Fields] OR "reporting"[All Fields] OR "reportings"[All Fields] OR "research report"[MeSH Terms] OR ("research"[All Fields] AND "report"[All Fields]) OR "research report"[All Fields] OR "report"[All Fields] OR "reported"[All Fields] OR "reports"[All Fields]) AND "no symptom*"[Text Word]

In this case, and for other combined keywords included in the

search, I would suggest the authors to consult the MeSH/Thesaurus and a Librarian for better search term inclusion based on keywords rather than phrases.

- The use of the field codes "MP" and "TW" is a bit confusing. The English databases included in the search all have different field code for the MeSH terms and I am not sure if "TextWords" even is an existing field in for example Embase. "MP" is not an existing field code in PubMed. Clear referral to which database host or platform the search has been conducted in is needed to allow full appraisal of the search.

- I also suggest the researchers to apply MeSH/Thesaurus terms directly form the Thesaurus. It is unlikely that the MeSH/Thesaurus terms are the same in all databases. Please consult a Librarian or information specialist for help.

The PRISMA checklist
- Item no. 5 is not reported. There is no indication in the manuscript that a protocol is registered or prepared for this review.

Minor suggestions:

Title: I wonder if geographical coverage and age/population groups could be specified in the title to make the inclusion more clear?

Abstract
I suggest that the authors add the search date and information about following the PRISMA guidelines in the Abstract.

116 Searching strategy
- Please indicate if the search strategy has been peer reviewed using for example the PRESS checklist (https://www.cadth.ca/resources/finding-evidence/press) or by a librarian, specialized in systematic review search methodologies.

207 Characteristics of studies and Subjects

- Please indicate how many or if no studies were found in the hand screening of reference lists described under "Search strategy"

Supplementary materials, figure 1:
- I suggest that the authors use and refer to the original PRISMA flow- diagram available on the PRISMA statement website.
Supplementary table 1: Search strategy for systematic review
- For full search transparency and reproducibility, I suggest that the authors specify the platforms/database host they conducted the search (OVID, Ebsco etc.), search date and eventual limitations for each database. Please note that it's not recommended to use a multi search tool or discovery tool for a systematic search. A much higher search precision is achieved when searching in the individual databases separately.

- There is, search technically speaking no need to include all variations of "asymptomatic" in "TextWords", if you search for "asymptomatic" only. This will include all variations. With the current lack of phrasing (see the comments under "major suggestions" above) for all search variations of "asymptomatic (Asymptomatic positive* etc.) a lot of irrelevant studies will be captured instead of

the search term variations intended.

VERSION 1 – AUTHOR RESPONSE

<u>**Reviewer: 1**</u>

Dr. Ivana Lapić, University Hospital Centre Zagreb Department of Laboratory Diagnostics

Comments to the Author:

The authors are to be congratulated on such a comprehensive analysis of published papers dealing with the asymptomatic ratio of COVID-19 cases.

Response: Thank you for the positive comments.

There are only some minor issues that should be addressed before the paper would be suitable for publication:

- Lines 93-100 - this part of the texts pertains more to the Materials and Methods section, and not Introduction

Response: We moved Line 93-100 to the Materials and Methods section (Line 142-150). Thank you.

- I suggest summarizing the data presented in the Supplementary table 1 in a few sentences or advantageously as a flowchart. In this form, it is hard to follow.

Response: Thank you for the valuable suggestion. We added the text description of Supplementary table 1 in the Methods section in line 125-132. We wrote:

"XC and ZH searched the Medline, Embase, PubMed, and three Chinese electronic databases (the Chinese National Knowledge Infrastructure [CNKI], WanFang Data, and VIP) from 1 November 2019 to 31 December 2020. The search string related to "COVID-19" AND "asymptomatic" was systematically developed in PubMed with the help of its MeSH terms, and was applied to all databases after discussing with an experienced Libationary (Maggie Choi). The search fields of "Text Word" was applied to ensure the best possible search evidence (Supplementary Table 1)."

- Paragraphs Literature screening and selection criteria, and Data extraction and subgrouping schemes should be shortened, maybe by merging some sentences/points

Response: Thank you for the valuable suggestion. We shortened the "Literature screening and selection criteria", and"Data extraction and subgrouping schemes paragraph" in Line 153-176. We wrote:

"All studies were screened by title and abstract first, followed by full texts if the study meets the inclusion criteria, which consist of: (1) the studying subjects were diagnosed with SARS-CoV-2 infection; (2) the study was designed as an observational study; and (3) the numbers of asymptomatic and symptomatic COVID-19 infections were explicitly and exactly reported.

The literature screening was conducted without language or region restriction. The exclusion criteria are as follows. They included (1) study that included patients without virological evidence of SARS-CoV-2 infection; exclusion criterion (2) study which did not investigate the distribution of asymptomatic COVID-19 infections among all subjects; (3) study that is not classified as original research, such as reviews, comments, case report; and (4) study has an overall sample size of less than 5."

- The first paragraph of the Results section repeats what is already stated in Figure 1. Such repetition should be avoided. Please use one way or another to present your results.

Response: We shorted the fist paragraph of the Results section to avoid duplications with Figure 1. The revised paragraph is:

"In total, 9,798 unique citations were identified in different databases by the literature search (Figure 1). We retrieved 661 full-text articles assessed for eligibility after 9,247 citations were excluded during title or abstract screening with pre-determined criteria. Finally, there were 240 articles included in the meta-analysis, among which 3 were additional records identified through reference list." **(Line 232-236)**

<u>**Reviewer: 2**</u>

Dr. Jean-Paul   Moatti, Aix-Marseille Universite

Comments to the Author:

Determining the rate of asymptomatic infection is key for epidemiological modelling of COVID 19 dissemination and for informing public health management of the health crisis. Since estimations of

such rate and its distribution according to patients characteristics has been quite heterogeneous through the numerous published studies, systematic review of the literature and quantitative meta-analysis are appropriate tools for providing appropriate estimates. Although some meta-analyses on this important topic have already been published, this one brings added value especially through the high number of included eligible studies.

Response: We thank the reviewer for his positive comments.

The process of identifying eligible studies and the use of the STATA "METAPROP" software are standard for such meta-analysis exercise but are implemented in a perfectly correct way.

Response: We thank the reviewer for his positive comments.

Minor revisions needed =

The last sentence of the abstract should be suppressed since the paper indeed provides no results to determine cost-effective strategies of identifying and tracing 61 asymptomatic infections.

Response: Thank you for the valuable suggestion. We deleted the misleading sentence and revised the Conclusion section in the Abstract as *"High proportion of asymptomatic infection were observed in pregnant women, children, adults aged no more than 45 years old, African residents, screening programmes, and in studies conducted in and after March 2020. Public health policies targeting these high-risk groups may be recommended to achieve early identification and more stringent containment of the pandemic."*

The distinction between screening and non screening studies should be further clarified.

Response: In line 189-192, we added a clarification on screening and non-screening studies. We wrote "Studies were categorized into 'screening' or 'non-screening' types by referring to the positive rate of SARS-CoV-2 pathogen test among included subjects. In the screening studies, the positive rate is less than 100%; while for non-screening studies, all subjects were tested positive." Thank you.

Due to the limited number of studies involved in the case of children and pregnant women, limitations of the meta-analysis in these two groups should be more emphasized in the Discussion section.

Response: Thank you for the valuable comments. As we extended our literature search to 31 December 2020, the number of studies on children increased from 10 to 30, while studies on pregnant women increased from 5 to 17 now. Still, we are aware of the limited number of longitudinal studies in this population. In the Discussion section, we clarified the limitation and wrote *"Nevertheless, we noted that 15 out of our 17 included studies on pregnant women are cross-sectional studies that in which the high proportion of asymptomatic infections may include both pre-symptomatic and asymptomatic cases. More follow-up studies among the pregnant women are needed before drawing further conclusions".* **(Line 345-349)**

The geographical heterogeneity of the estimated rates (with higher rates in European studies) should be further discussed (including the role of differences in health systems and access).

Response: Thank you for the very helpful suggestion. As we updated our literature search to 31 December 2020, the increased number of publications gave us the chance to conduct subgroup estimation of five continents, and the results showed that asymptomatic ratio in Africa was even higher than that in Europe. In the fifth paragraph of the Discussion section, we further discussed the geographical heterogeneity of the estimated rates. We wrote *"Our results also showed that estimated ratio in Asia is the lowest among all continents. Possible explanations were summarized in a published meta-analysis, from the perspectives of infection control policies and host characteristics. Meanwhile, the rates in Africa (64.3%) was the highest among all continents, although the limited number of subjects (20,271 COVID-19 infections) in African studies reminded us to think twice before generalizing the results. The phenomenon may be partly explained by a few factors in African patients, including the generally younger age, the lower proportion of chronic disease patients and elderlies living in nursing homes, and the higher serum Vitamin D levels due to rich sun exposure. Despite the higher asymptomatic ratio, it is noted that Africa is the continent with the lowest RT-PCR testing rate as well as the lowest vaccination rate. The high proportion of asymptomatic ratio may further hinder the timely detection and control of COVID-19 infections."*

<u>**Reviewer: 3**</u>

Dr. Benjamin Bowe, Saint Louis University

Comments to the Author:

The rates of asymptomatic COVID-19 are important to know for public health officials, but something quite difficult to answer. While there are several reviews and meta-analyses on this subject, given possible spatiotemporal heterogeneity, and differences by other factors such as age, continued evaluation and investigation of population specific rates may be informative.

Response: Thank you for the positive comments.

I have a few comments for consideration:

Given that the last study included here was published in July of last year, perhaps there might be an opportunity to update incorporated information to help derive estimates that are more current, considering the dynamicity of the pandemic, to enhance novelty.

Response: We agree to the reviewer's idea and updated the included studies to 31 December 2020, in order to provide more comprehensive understanding on this issue throughout a longer period. Please kindly check our updated findings. Thank you.

Along those lines, the authors note the limitations of using cross-sectional analyses. Updating the data might provide enough information to limit analyses to longitudinal studies. Alternatively, the authors might consider weighting by risk of bias.

Response: Thank you for pointing out this very important issue. By updating the inclusion criteria to 31 December 2020, our review included 105 more studies. Meanwhile, the proportion of longitudinal study now increased to 11.7% among all the included studies. This can provide more reliable information on the asymptomatic ratio.

Generally, observational study participants will get tested for a reason; this is very likely to bias results (asymptomatic less likely to seek getting tested), and is not really discussed.

Response: Thank you for pointing out this important limitation of our study. We discussed the possible bias caused by observational studies in the last paragraph of the Discussion section. We wrote *"…our meta-analysis focused on real-world evidence and observational studies, in which subjects with more severe and easily-recognized symptoms are more likely to be selected. The collider bias caused by non-representative sampling strategies (such as sampling conditional on testing and prognosis conditional on hospitalization) in existing observational studies on COVID-19 has been deeply discussed in (34).* (Line 409-414)

We are also aware that people may get tested for varied reasons associated with the social and political factors in each region, yet most studies did not report subjects' motivation of getting tested. We discussed this in the Discussion section, we wrote that *"… people may get tested for varied reasons associated with the social, cultural, and political factors in each*

region. For instance, frontline health workers and people with a history of exposure were in general more likely to be reported in screening programmes, while the samples in non-screening studies were likely to be dominated by subjects having severe symptoms requiring hospitalization." **(Line 367-372)**

Reference: 34. Griffith GJ, Morris TT, Tudball MJ, Herbert A, Mancano G, Pike L, et al. Collider bias undermines our understanding of COVID-19 disease risk and severity. Nature communications. 2020;11(1):5749.

Subgroup analysis by "screening" status uses a limited definition that could mean a lot of different things across the studies, so is not super clear the actual implication there.

Response: We thank the reviewer for his valuable comments, and further clarified the definitions and differences of screening and non-screening studies in the Methods section. We wrote *"Studies were categorized into 'screening' or 'non-screening' types by referring to the positive rate of SARS-CoV-2 pathogen test among included subjects. In the screening studies, the positive rate is less than 100%; while for non-screening studies, all subjects were tested positive."*

<u>**Reviewer: 4**</u>

Mrs. Linda Östlundh, United Arab Emirates University College of Medicine and Health Sciences

Comments to the Author:

Below is a review of the methods part of the paper only. The peer review excludes the search strategies applied in the Chinese databases due to lack of language skills.

The reporting of the search method of this review is very structured and follows the PRISMA guidelines. A copy of the search strategy applied in all databases is appended to the review and the authors have used a combination of MeSH terms and TextWords in the searches. However, a search technical enhancement of the search strategies is needed in order for the researcher to ensure that the search retrieves a result that ensure that the review is based on the best available evidence for this topic.

Response: We thank the reviewer for the valuable comment on searching strategy, and revised point-by-point according to the detailed suggestions below.

Major suggestions:

116 Searching strategy

- Considering the rapid development of the research field of COVID-19, the fact that the result mainly includes studies from US and China and that the literature search for this review is conducted in July, 2020, I strongly suggest that the authors update the search.

Response: Thank you for pointing out this issue. We updated the included studies to 31 December 2020.

- Please specify who of the authors conducted the search

Response: In the Methods section, we clarified that "XC and ZH searched the Medline, Embase, PubMed, and three Chinese electronic databases (the Chinese National Knowledge Infrastructure [CNKI], WanFang Data, and VIP) from 1 November 2019 to 31 December 2020". Thank you.

- Information about the search strategy used including eventual filters or limitations (or the exclusion of such) applied for the search is needed.

Response: Thank you for the questions. We have clarified that no filters or limitations were applied to ensure the inclusion of pre-indexed materials, which has been added the article. (Line 132-133)

- Please specify "highly relevant references". Are those the finally included papers? Who selected and conducted the screening of these reference lists?

Response: Thank you for the questions. We clarified that "highly relevant references" means "reference lists from several highly relevant articles" (Line xxx-xxx). We also specified that "highly relevant references were also searched (by XC and ZH) by reviewing the reference list of the included articles" (Line 134-135).

Literature screening and selection criteria

- Please specify any software or reference management tool was used in the screening or if the screening was conducted by hand?

Response: We clarified in the Methods section that "All manuscripts were imported into the Endnote software (version X8, Thomson Reuters, Carlsbad, California) to store and manage the retrieved citations." (Line 137-139).

- Line 146: please specify if the "studies that analyzed the same group of subjects more than once" but with a larger population included, reports on the same measure / have the same research question?

Response: Sorry for the misleading wordings. We revised the sentence as "For the same group of subjects been reported by different articles, only articles with the most updated and detailed information were included for further analysis."

463- References

- The reference to the PRISMA statement is to the PRISMA P (protocol) reporting guidelines. Please apply and refer to the PRISMA statement for Systematic Reviews and Meta-analysis instead.

Response: Thanks for your review. We updated the mauscript by applying and referring to the PRISMA statement for Systematic Reviews and Meta-analysis:

14. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS medicine. 2009;6(7):e1000097.

Supplementary table 1: Search strategy for systematic review

- I would suggest the researchers to develop the inclusion of search-term variation in the "TextWord" search. This will enhance the search result and ensure that the best possible evidence is located. A tip is to have a look at the "entry terms" in PubMed's Mesh where additional search variations for "COVID-19" and "asymptomatic" is available. This will help the authors to a systematic search term inclusion.

Response: Thanks for your helpful suggestion. We followed the suggestion and searched the "entry terms" in PubMed's MeSH. Based on the search results, we now included more terms

(such as "Inapparent Infection" and "Subclinical Infection") into our "TextWord" search. Please kindly refer to our revised Supplymentary Table 1 for more details.

- Phrasing of the keywords is missing (applies to most databases). By applying quotation marks ("Reported no symptom*") to the keywords that includes more than one search term, the specific term will be searched. A search without quotation marks generates a totally different and irrelevant result. A search on: Reported no symptom* in PubMed using the TextWord field generates 5,128 references (with no filter applied) while adding quotation marks retrieves 0 references. When phrasing is left out, the database translates the request automatically which mostly results in an irrelevant translation. The PubMed translation for the example below is as follows:

Search: Reported no symptom*[Text Word]

("reportable"[All Fields] OR "reporting"[All Fields] OR "reportings"[All Fields] OR "research report"[MeSH Terms] OR ("research"[All Fields] AND "report"[All Fields]) OR "research report"[All Fields] OR "report"[All Fields] OR "reported"[All Fields] OR "reports"[All Fields]) AND "no symptom*"[Text Word]

In this case, and for other combined keywords included in the search, I would suggest the authors to consult the MeSH/Thesaurus and a Librarian for better search term inclusion based on keywords rather than phrases.

Response: Thanks for your suggestions. We consulted Ms. Maggie Choi, Librarian in Li Ping Medical Library, The Chinese University of Hong Kong, for the search term inclusion based on keywords rather than phrases. We clarified this in the Method section, and acknowledged Ms. Maggie Choi for her valuable help.

- The use of the field codes "MP" and "TW" is a bit confusing. The English databases included in the search all have different field code for the MeSH terms and I am not sure if "TextWords" even is an existing field in for example Embase. "MP" is not an existing field code in PubMed. Clear referral to which database host or platform the search has been conducted in is needed to allow full appraisal of the search.

Response: Thanks for your kind remind. "COVID-19" and "asymptomatic" related terms have been searched in PubMed's Mesh, and "TW" rather than "MP" were used in our search strategy, which has been displayed in Supplementary table 1.

- I also suggest the researchers to apply MeSH/Thesaurus terms directly form the Thesaurus. It is unlikely that the MeSH/Thesaurus terms are the same in all databases. Please consult a Librarian or information specialist for help.

Response: Thanks for your kind suggestions. We revised our search strategy accordingly, and in the Method section, we clarified "*The search string related to "COVID-19" AND "asymptomatic" was systematically developed in PubMed with the help of its MeSH terms, and was applied to all databases after discussing with an experienced Libationary (Maggie Choi). The search fields of "Text Word" was applied to ensure the best possible search evidence.*"

The PRISMA checklist

- Item no. 5 is not reported. There is no indication in the manuscript that a protocol is registered or prepared for this review.

Response: Thanks for your kind remind. We clarify that no protocol was registered or prepared for this review.

Minor suggestions:

Title: I wonder if geographical coverage and age/population groups could be specified in the title to make the inclusion more clear?

Response: Thank you for the kind suggestion. We revised the title as "*Rate of asymptomatic COVID-19 among ascertained infections in different region and population groups: A systematic review and meta-analysis including 130,123 infections from 241 studies*".

Abstract

I suggest that the authors add the search date and information about following the PRISMA guidelines in the Abstract.

Response: Thanks four your suggestions. We have already added the search date and information about following the PRISMA guidelines in the Abstract part. We wrote "*This systematic review and meta-analysis was conducted according to the standards strictly following the 'Preferred Reporting Items for Systematic reviews and Meta-Analyses' (PRISMA) guideline.* "

116 Searching strategy

- Please indicate if the search strategy has been peer reviewed using for example the PRESS checklist (https://www.cadth.ca/resources/finding-evidence/press) or by a librarian, specialized in systematic review search methodologies.

Response: Thanks for your kind remind. Search strategy has been peer reviewed using for example the PRESS checklist. We also consulted a librarian before conducting the search.

207 Characteristics of studies and Subjects

- Please indicate how many or if no studies were found in the hand screening of reference lists described under "Search strategy"

Response: In Figure 1, we specified that there are 3 studies found by the hand screening of reference lists. Thank you.

Supplementary materials, figure 1:

- I suggest that the authors use and refer to the original PRISMA flow- diagram available on the PRISMA statement website.

Response: Thanks for your suggestion. We have revised our flow-diagram on the original PRISMA flow-diagram.

Supplementary table 1: Search strategy for systematic review

- For full search transparency and reproducibility, I suggest that the authors specify the platforms/database host they conducted the search (OVID, Ebsco etc.), search date and eventual limitations for each database. Please note that it's not recommended to use a multi search tool or discovery tool for a systematic search. A much higher search precision is achieved when searching in the individual databases separately.

Response: Thanks for your kind reminder. We double checked and confirmed that the multi search tool and discovery tool were not used. We searched individual databases seperately to achieve a higher search precision.

- There is, search technically speaking no need to include all variations of "asymptomatic" in "TextWords", if you search for "asymptomatic" only. This will include all variations. With the current lack of phrasing (see the comments under "major suggestions" above) for all search variations of "asymptomatic (Asymptomatic positive* etc.) a lot of irrelevant studies will be captured instead of the search term variations intended.

Response: Thanks for your kind suggestions. PubMed's MeSH were used to search related terms for "COVID-19" and "asymptomatic". A Librarian from The Chinese University of Hong Kong was consultant to improve our search strategy. Please kindly refer to Supplementary Table 1 for the updated strategy.

VERSION 2 – REVIEW

REVIEWER	Linda Östlundh United Arab Emirates University College of Medicine and Health Sciences, National Medical Library
REVIEW RETURNED	01-Jul-2021

GENERAL COMMENTS	Below is a methods peer review only. It is a pleasure to get the opportunity to review this very well reported systematic review about rate of asymptomatic COVID-19 among ascertained infections in 2 different region and population groups. The review follows the PRISMA statement even if there is a lack of a pre-registered or prepared protocol. The search strategies and results from all included databases are transparent reported for the best possible reproducibility (review of the English search only) and a detailed PRISMA flow-diagram illustrates the search result, deduplication, and the blinded selection process. The researchers have covered all required reporting items and appended a PRISMA checklist. Methodological speaking, this is a very good, reported paper. I only have a few suggestions for the authors: Major suggestions: -Even if the study includes a good set of paper and the search was conducted in December 2020, I advise the authors to conduct a search update. The volume of COVID-19 related research grows in a high speed and a lot has happened between December last year and today's date. A search update would increase the timeliness and clinical usefulness of the paper. Minor suggestions:

	- It would be helpful for non-Chinese speakers to now wheat type of Chinese databases that are included (subject area, type of sources: peer reviewed and/or grey etc.). - If none of the Chinese databases are grey sources, it would be helpful with a short line justifying the exclusion of grey materials in in this study. A suggestion for future reviews is to use a systematic review software such as Covidence (free first review) or Rayyan (free) for de-duplication and screening. This saves time compared to screening in a reference management tool and you can report on a blinded screening process set by the software in your review.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 4

Mrs. Linda Östlundh, United Arab Emirates University College of Medicine and Health Sciences

Comments to the Author:

Below is a methods peer review only.

It is a pleasure to get the opportunity to review this very well reported systematic review about rate of asymptomatic COVID-19 among ascertained infections in 2 different region and population groups.

The review follows the PRISMA statement even if there is a lack of a pre-registered or prepared protocol. The search strategies and results from all included databases are transparent reported for the best possible reproducibility (review of the English search only) and a detailed PRISMA flow-diagram illustrates the search result, deduplication, and the blinded selection process. The researchers have covered all required reporting items and appended a PRISMA checklist.

Methodological speaking, this is a very good, reported paper. I only have a few suggestions for the authors:

Response: We thank the reviewer for her positive comments.

Major suggestions:

-Even if the study includes a good set of paper and the search was conducted in December 2020, I advise the authors to conduct a search update. The volume of COVID-19 related research grows in a high speed and a lot has happened between December last year and today's date. A search update would increase the timeliness and clinical usefulness of the paper.

Response: Thank you for pointing out this important question. We insist to keep the search period before year 2021 for two main reasons:

a). Mass vaccination campaigns against COVID-19 implemented globally in year 2021 have been shown to reduce symptomatic infection and transmission;

b). A few major mutations of the virus were observed in year 2021, while the association between asymptomatic infection and different virus mutations remained unclear.

Hence, after consulting a few experts in infectious disease, we would keep our literature search period within year 2019-2020.

To make it clear, we added the time limit to our manuscript title. The update title is "*Rate of asymptomatic COVID-19 among ascertained infections in different region and population groups in 2020: A systematic review and meta-analysis including 130,123 infections from 241 studies*".

Minor suggestions:

- It would be helpful for non-Chinese speakers to now what type of Chinese databases that are included (subject area, type of sources: peer reviewed and/or grey etc.).

Response: Thank you for the kind reminder. We added a short description of these Chinese database in the method section. We wrote:

"*CNKI, WanFang Data, and VIP are affiliates of the Chinese Ministry of Science & Technology that providing access to peer reviewed, continuously updated research journal articles in Chinese.*"

- If none of the Chinese databases are grey sources, it would be helpful with a short line justifying the exclusion of grey materials in in this study.

Response: We thank the reviewer for bring out this important issue on grey literature, and also noted the importance of grey literature. When widely available literature was representative, there would be little need to include grey literature (Conn et al., 2003). With a long search period of over one year, and a total of 241 included studies, we decided not to include grey literature. The Egger's test also detected no publication bias in our included studies. Hence, we decided not to include grey literature in our review.

Reference: Conn VS, Valentine JC, Cooper HM, Rantz MJ. Grey literature in meta-analyses. Nursing research. 2003 Jul 1;52(4):256-61.

A suggestion for future reviews is to use a systematic review software such as Covidence (free first review) or Rayyan (free) for de-duplication and screening. This saves time compared to screening in a reference management tool and you can report on a blinded screening process set by the software in your review.

Response: Thank you very much for this important suggestion. We will explore the software when doing further studies.