PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Risk factors for COVID-19 infection, disease severity and related deaths in Africa: a systematic review
AUTHORS	Gesesew, Hailay; Koye, Digsu Negese; Fetene, Dagnachew; Woldegiorgis, Mulu; Kinfu, Yohannes; Geleto, Ayele; Melaku, Yohannes Adama; Mohammed, Hassen; Alene, Kefyalew; Awoke, Mamaru; Birhanu, Mulugeta; Gebremedhin, Amanuel; Gelaw, Yalemzewod; Shifti, Desalegn Markos; Muluneh, Muluken; Tegegne, Teketo; Abrha, Solomon; Aregay, Atsede; Ayalew, Mohammed; Gebre, Abadi; Gebremariam, Kidane; Gebremedhin, Tesfaye; Gebremichael, Lemlem; Leshargie, Cheru; Kibret, Getiye; Meazaw, Maereg; Mekonnen, Alemayehu; Tekle, Dejen; Tesema, Azeb; Tesfay, Fisaha; Tesfaye, Wubshet; Wubishet, Befikadu; Dachew, Berihun; Adane, Akilew

VERSION 1 – REVIEW

REVIEWER	Dervla Kelly University of Limerick, Ireland
REVIEW RETURNED	01-Oct-2020

GENERAL COMMENTS	Overall: Worthwhile topic to identify risk factors forCOVID-19 in Africa. Sound, well executed methodology. Implications of findings could be translated into some suggested future steps for researchers. Abstract Line 33 typo severe is should be reflected here. Strengths and Weaknesses This section seems a little rushed and light on substance. Page 4 Line 9 "entire spectrum of COVID": think focus is on severe forms of COVID so should reflect this. Page 4 line 10: lacking detail on breath and types of proposed multidisciplinary approaches Introduction Line 21: 30,00 deaths: check number Methods Data Extraction: Line 10: Was there any quality check on data extraction? Figure 1: writing text box obscured. Please fix. Discussion Page 17 Line 27: phrasing "have an open economy" rephrase so flows better. Page 18: Line 14: what types of research? Some specific examples of gaps found in research and implications for future work would be nice. More data collection needed? Hospital/community/population level data?

REVIEWER	SALMON Dominique

	University of Paris, France HOTEL DIEU Hospital, Paris , France
REVIEW RETURNED	04-Oct-2020

GENERAL COMMENTS	The authors have conducted a systematic review of the literature to synthetize existing evidence on risk factors affecting COVID-19 across Africa. It is an original approach. The methodology is clearly defined and detailed. However, the conclusions drawn by the authors are too affirmative. A large set of data is issued from modelling studies, where the results are known to be approximative depending on the accuracy of observations and the precisions parameters in the model. If the demographics, health system, politico-economic factors, behaviors and interactions between people seem to be issued on real observations, it is not the same for clinical variables. No study has demonstrated for example that HIV was a risk factor for severe COVID. And in the few HIV studies focused on the determinants the severity of the cases, classical factors such as age, sex, metabolic syndrome and hypertension were involved but not the immune deficit. It is the same for anemia and TB which have been put in a model without any background data concerning their potential implication the severity of the COVID. Other comments: Methods: The authors define severity as hospital admission and high risk of death. Such a definition does not correspond to the currently accepted criteria of severity that relies in WHO. Criteria on oxygen requirement, admission in intensive care units or death. Hospitalization is not a sufficient criteria as in some countries, all symptomatic patients at the beginning of the epidemy are systematically hospitalized to avoid transmission. Risk factor for severity is what the authors are looking for and can not be include in the criteria of severity. Results: There is one paragraph on the description of the study but no paragraph on the synthesis of the results Discussion: The authors should analyze with more criticism the published studies and should use the conditional time and not the imperfect time. Moreover, we face a viral highly transmissible infection. It is important to note that all the measures will delay the infection but will not allow to avoid it. Finally, the present results drawn for Africa should be compared to those drawn for other continents, mainly continents with similar socio economic levels such as South Asia (important results have been issued for Indonesia) and South America. What are the similarities and the differences? Table 1 should be reviewed especially the last right column to clarify the messages, improve English and avoid repetitions. Tables should not be inside the text but at this end Figure 1: content of the right squares is not readable

REVIEWER	Eric Shah, MD Dartmouth Hitchcock Medical Center, USA
REVIEW RETURNED	14-Nov-2020

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GENERAL COMMENTS	This was a systematic review has been conducted to synthesize existing evidence on risk factors affecting COVID-19 outcomes across Africa. Statistical plan is appropriate to the proposed work and adheres to PRISMA.
	Because the body of evidence here is so new, I wonder if the authors should actually rename this as a "scoping review" still while following PRISMA. Otherwise this represents a technically well-done study in an area with scant evidence. This is only a minor point, so will defer to the editors and/or authors if they disagree.

VERSION 1 – AUTHOR RESPONSE

Reviewers' reports:

Reviewer (R1): 1

Reviewer Name: Dervla Kelly

Institution and Country: University of Limerick, Ireland

Please state any competing interests or state 'None declared': None declared

Reviewer 1 comment 1 (R1C1):

Overall: Worthwhile topic to identify risk factors forCOVID-19 in Africa. Sound, well executed methodology. Implications of findings could be translated into some suggested future steps for researchers.

Reply to Reviewer 1 comment 1 (R1R1):

First, we are truly grateful for putting your valuable time to review our work. We thank you also for the feedback and input that you have provided on the paper. All comments have been addressed as shown below.

R1C2: Abstract, Line 33 typo severe is should be reflected here.

R1R2: The typo error has been corrected.

R1C3: Strengths and Weaknesses. This section seems a little rushed and light on substance.

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R1R3: We have revised the section for clarity and content in accordance with the Journal's guideline.

R1C4: Page 4 Line 9 "entire spectrum of COVID": think focus is on severe forms of COVID so should reflect this.

R1R4: Yes, our paper covers sever forms of COVID, but we have also assessed the evidence on infection and mortality more broadly. This was why the phrase 'entire spectrum of COVID' was used in the paper.

R1C5: Page 4 line 10: lacking detail on breath and types of proposed multidisciplinary approaches

R1R5: Thank you for the observation. However, we note that the contents of the 'strengths and limitations section' were informed by the journal's guideline; it only allows a single statement, up to a maximum of five bullets, with a focus on key aspects of the paper.

R1C6: Introduction, Line 21: 30,00 deaths: check number

R1R6: This is now revised to 21 Nov 2020.

R1C7: Methods, Data Extraction: Line 10: Was there any quality check on data extraction?

R1R7: As reported on page 8 (the third line from below), methodological quality and risk of bias in included studies were assessed using JBI tools.

R1C8: Figure 1: writing text box obscured. Please fix.

R1R8: We have addressed the issue.

R1C9: Discussion, Page 17 Line 27: phrasing "have an open economy" rephrase so flows better.

R1R9: The text has been rephrased.

R1C10: Page 18: Line 14: what types of research? Some specific examples of gaps found in research and implications for future work would be nice. More data collection needed? Hospital/community/population level data?

R1R10: The following sentence has been inserted in the revised paper (page number 17, last sentence of second paragraph). "Most importantly, given the high burden of HIV and malaria in the Africa region the molecular, genetic, clinical and environmental implications of COVID-19 on people living with HIV and malaria should be explored in greater detail."

We have also included the following sentence: "Future research on COVID-19 in the region and beyond should focus on robust epidemiological study designs that are suitable to capture causal relationships and long term impacts of the disease." in the last paragraph of the discussion section of the paper.

Reviewer (R2): 2

Reviewer Name: SALMON Dominique

Institution and Country: University of Paris, France; HOTEL DIEU Hospital, Paris , France.

Please state any competing interests or state 'None declared': None

Reviewer 2 comment 1 (R2C1):

The authors have conducted a systematic review of the literature to synthetize existing evidence on risk factors affecting COVID-19 across Africa. It is an original approach. The methodology is clearly defined and detailed. However, the conclusions drawn by the authors are too affirmative. A large set of data is issued from modelling studies, where the results are known to be approximative depending on the accuracy of observations and the precisions parameters in the model.

Reply to Reviewer 2 comment 1 (R2R1):

First, we would like to thank you for your valuable time, for your favourable assessment of our paper, and for the important feedback and input that you have provided to us. All comments have been addressed as shown below

R2C2: If the demographics, health system, politico-economic factors, behaviors and interactions between people seem to be issued on real observations, it is not the same for clinical variables. No study has demonstrated for example that HIV was a risk factor for severe COVID. And in the few HIV studies focused on the determinants the severity of the cases, classical factors such as age, sex,

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metabolic syndrome and hypertension were involved but not the immune deficit. It is the same for anemia and TB which have been put in a model without any background data concerning their potential implication the severity of the COVID.

R2R2: Thank you for the observation. This remains the main limitation of existing literature as the available evidence rests on cross-sectional and cross-country data. Such studies as we all are aware of do not suggest casual relationships, and we have indicated this in the strength and limitation section as being the main limitation of the present systematic review.

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Other comments:

R2C3: Methods: The authors define severity as hospital admission and high risk of death. Such a definition does not correspond to the currently accepted criteria of severity that relies in WHO. Criteria on oxygen requirement, admission in intensive care units or death. Hospitalization is not a sufficient criteria as in some countries, all symptomatic patients at the beginning of the epidemy are systematically hospitalized to avoid transmission. Risk factor for severity is what the authors are looking for and can not be include in the criteria of severity.

R2R3: As knowledge about COVID and relevant data on the disease are still evolving, a broader definition of severity has been adopted. Most of the key terms you mentioned about are, for example, included in the search strategy. However, we have also inserted the following statement (on page 18, second paragraph) to bring clarity to the issue, and caution readers about our findings.

"Second, we have used hospital admission as one of the indicators of severity, but this may not be a sufficient criteria given that in some countries, especially in the early stage of the pandemic, all symptomatic patients were systematically hospitalized to avoid transmission."

R2C4: Results: There is one paragraph on the description of the study but no paragraph on the synthesis of the results.

R2R4: As the interest of the paper is on risk factors of the entire spectrum of COVID, we have put the

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synthesis of these risk factors in the section titled 'factor affecting COVID-19 infection, severity, and related deaths'. Table 1 provides a summary of the findings on each of these elements.

R2C5: Discussion: The authors should analyze with more criticism the published studies and should use the conditional time and not the imperfect time.

R2R5: This comment is not clear, specially what is meant by 'conditional and no 'imperfect' time'. We would be very happy to address the point, if the reviewer clarifies their comment.

R2C6: Moreover, we face a viral highly transmissible infection. It is important to note that all the measures will delay the infection but will not allow to avoid it.

R2R6: Yes, we agree with the reviewer. Our review has captured the available information at the time of writing up of this paper. However, to bring clarity to the matter, we have now included the following statement in the conclusion section (see last paragraph).

"However, it should be noted that even with a complete adherence to such public health measures, governments can only expect to mitigate the spread of the virus in the region. Eventually, safe, and effective vaccines and drugs are required to end this pandemic.

R2C7: Finally, the present results drawn for Africa should be compared to those drawn for other continents, mainly continents with similar socio economic levels such as South Asia (important results have been issued for Indonesia) and South America. What are the similarities and the differences?

R2R7: We agree with the reviewer. We have already included global studies that included some African data in this review and we also compared our findings with other countries experiences such as China (see, for example, Page 17, last paragraph). We have now also included the study from Indonesia in various part of the discussion section of our paper (For example, see Page 16, par 2, last sentence, and Page 17, line #4).

R2C8: Table 1 should be reviewed especially the last right column to clarify the messages, improve English and avoid repetitions.

R2R8: The content has been reviewed for clarity.

R2C9: Tables should not be inside the text but at this end

R2R9: We stand corrected, but we feel BMJ advises authors to embed tables within the main text.

R2C10: Figure 1: content of the right squares is not readable

R2R10: We have re-formatted the figure for improved readability.

Reviewer (**R3**): 3

Reviewer Name: Eric Shah, MD

Institution and Country: Dartmouth Hitchcock Medical Center, USA

Please state any competing interests or state 'None declared': None declared

Reviewer 3 comment 1 (R3C1):

This was a systematic review has been conducted to synthesize existing evidence on risk factors affecting COVID-19 outcomes across Africa. Statistical plan is appropriate to the proposed work and adheres to PRISMA.

Because the body of evidence here is so new, I wonder if the authors should actually rename this as a "scoping review" still while following PRISMA. Otherwise this represents a technically well-done study in an area with scant evidence. This is only a minor point, so will defer to the editors and/or authors if they disagree.

Reply to Reviewer 3 comment 1 (R3R1):

Very many thank you for your valuable time, for your favourable assessment of our paper, and for the suggestion on the title of the paper.

It is true that the evidence presented in our paper is so new, but as you may agree with us even in established areas of science knowledge tends to evolve with time. Given that our review captures all relevant and available evidence at the time and we have applied established systematic review procedures as opposed to scoping reviews, we prefer to leave the title as is.

VERSION 2 – REVIEW

REVIEWER	Dervla Kelly University of Limerick, Ireland
REVIEW RETURNED	16-Dec-2020

GENERAL COMMENTS	Thanks to the authors. All my comments have been addressed. I had one further comment regarding the limitations of the 7 modelling studies included in the review. Do the authors think there are any limitations to these studies that should be noted?

VERSION 2 – AUTHOR RESPONSE

Reviewer 1 comments	Reply
My thanks to the authors. All my comments have been addressed.	Thank you for your contribution.
I have one further comment regarding the limitations of the 7 modelling studies included in the review. Do the authors think there are any limitations to these studies that should be noted?	Thank you for raising this. We have added the limitation in page 17. We revised the statement as …" Fourth, there is still limited evidence on COVID-19 in countries Africa (some of the included studies are even pre-print and others are modelling based studies) and the review was unable to provide a stratified analysis by regions—authors of the modelling studies have already noted some limitations of the modelling studies."

NB. We would like to note to the editor that:

1) We have revised the COVID-19 data as of 10 Jan. 21 in page 4
2) We have updated some of the pre-print materials as they are published now— we have checked that there is no difference in contents.