PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The impact of carbapenem resistance on mortality in patients infected with Enterobacteriaceae: a systematic review and meta-analysis
AUTHORS	Zhou, Ruyin; Fang, Xiangming; Zhang, Jinjin; Zheng, Xiaodong; Shangguan, Shuangyue; Chen, Shibo; Shen, Yingbo; Liu, Zhihai; Li, Juan; Zhang, Rong; Shen, Jianzhong; Walsh, Timothy R; Wang, Yang

VERSION 1 – REVIEW

REVIEWER	Rigatto, M. Hospital São Lucas da PUCRS
REVIEW RETURNED	26-Jul-2021

GENERAL COMMENTS	The manuscript entitled "The impact of carbapenem resistance on mortality in patients infected with Enterobacteriaceae: a global systematic review and meta-analysis" evaluates the mortality impact of carbapenem-resistant Enterobacteriaceae (CRE) versus carbapenem-susceptible Enterobacteriaceae (CSE) infections through an updated systematic review and meta-analysis on the topic. The article is very well written and does a stratified analysis and meta-regression according to infection type, geographic region, sample size and year of publication, which brings valuable insights to the topic. Some points, however, could be better clarified/discussed on the text: - The studies included patients from different settings and used different time points to evaluate mortality. For example, the only study conducted in Africa evaluated mortality in the ICU. If this study is focusing specifically in critical care patients, it is expected to find higher mortality rates when compared to patients at clinical ward treated for less severe infections. Therefore, any conclusions taken when comparing mortality in Africa with other continents should take this in account. According to table 1, from the 9 studies done in Europe, only three evaluated in-hospital mortality while the others used 14, 21, 28 or 30-day mortality as final endpoints. Comparing mortality with different follow-periods can lead to biased conclusions. It would be interesting to do a subgroup analysis including only studies that had in-hospital mortality as a stablished endpoint or to do a time-to-mortality analysis if this information is available. The mortality definition is also a concern when comparing infections from different sites. The one study that evaluated neurosurgical infections used mortality attributable to infection as an endpoint. This can hardly be compared to general in-hospital mortality rates in CRE or CSE

groups. All these points could be better explored and discussed in the text.
- The literature search was conducted for articles published from 1994 to 2020, however the earlier study published in this meta-analysis was from 2008. Didn't any of the studies published in the first 14 years of search met the inclusion criteria? Why was that? Authors could make a brief comment on that.
- In tables 2, 3 and 4 it would be useful to provide not only the number of studies included but also the number of patients in each subgroup.
- The authors mention on lines 22-25 that "Our study also has several limitations. Firstly, we only include two clinically important Enterobacteriaceae species, Klebsiella pneumoniae and Escherichia coli." The nine studies that included "Mixed Enterobacteriaceae pathogens" were also restricted to these two species? That was not very clear to me.
- On the discussion section, lines 17-23, authors mention that "to both high mortality rates in patients (61.1%) and CSE patients (51.7%) reported in only one study in Africa, which might be related to the low level of medical care and poor hygiene." Is there any objective evidence of low level of medical care and poor hygiene contributing to higher mortality in the setting this study took place? A reference should be added or the authors should explain better this hypothesis.

REVIEWER	Peng, Limin Emory University
REVIEW RETURNED	18-Sep-2021

| GENERAL COMMENTS | Comments on manuscript ``The Impact of carbapenem resistance on mortality in patients infected with Enterobacteriaceae: a global systematic review and meta-analysis"

This manuscript is very well written with clearly described study design, appropriate statistical analyses, and thorough interpretations of analysis results. The meta analysis presented in this manuscript provides valuable information to help understand the impact of carbapenem resistance on mortality in patients infected with Enterobacteriaceae, and its heterogeneity potentially contributed by factors such as economic status or geographic regions. The following are several minor comments that the authors may consider to incorporate in the revision of the manuscript.

1.   The mortality outcomes adopted in the presented meta analysis take a variety of forms. The choice of the mortality outcome can potentially influence the rate of mortality reported in different studies. For example, 30-day mortality may tend to capture more cases of deaths as compared to 6-day mortality. It is worth some discussions on the potential limitation related to equally accounting for all kinds of measurements of mortality. Categorizing mortality measurements into a few groups and conducting analyses stratified by the mortality outcome type may help address the potential effect heterogeneity caused by this factor.

2.   Page 10: I suggest including the interpretation of RR>1 (or 1) or RD>0 (or <0), in addition to the interpretation of RR of 1 and RD of 0. |

	3. Page 10: I suggest changing the words "statistically significant" in "considered statistically significant when I2 values > 50%" to words such as "high" or "substantial".
	4. The title of Figure 4 is not properly shown and needs to be fixed.

VERSION 1 – AUTHOR RESPONSE

Response to Reviewer 1's Comments:

Reviewer 1: Comments to the Author:

The manuscript entitled "The impact of carbapenem resistance on mortality in patients infected with Enterobacteriaceae: a global systematic review and meta-analysis" evaluates the mortality impact of carbapenem-resistant Enterobacteriaceae (CRE) versus carbapenem-susceptible Enterobacteriaceae (CSE) infections through an updated systematic review and meta-analysis on the topic. The article is very well written and does a stratified analysis and meta-regression according to infection type, geographic region, sample size and year of publication, which brings valuable insights to the topic. Some points, however, could be better clarified/discussed on the text:

1- The studies included patients from different settings and used different time points to evaluate mortality. For example, the only study conducted in Africa evaluated mortality in the ICU. If this study is focusing specifically in critical care patients, it is expected to find higher mortality rates when compared to patients at clinical ward treated for less severe infections. Therefore, any conclusions taken when comparing mortality in Africa with other continents should take this in account. According to table 1, from the 9 studies done in Europe, only three evaluated in-hospital mortality while the others used 14, 21, 28 or 30-day mortality as final endpoints. Comparing mortality with different follow-periods can lead to biased conclusions. It would be interesting to do a subgroup analysis including only studies that had in-hospital mortality as a stablished endpoint or to do a time-to-mortality analysis if this information is available. The mortality definition is also a concern when comparing infections from different sites. The one study that evaluated neurosurgical infections used mortality attributable to infection as an endpoint. This can hardly be compared to general in-hospital mortality rates in CRE or CSE groups. All these points could be better explored and discussed in the text.

● *Response: We greatly appreciate the reviewer's careful review and helpful suggestion. We agree with the Reviewer's comment concerning the issue that comparing mortality with different measurements may lead to biased conclusions. In the revised manuscript, we categorized the mortality outcomes with different definitions or different follow-periods into eight types, and all the comparisons were undertaken based on the same mortality type. In the primary meta-analysis, we evaluated the pooled RR and RD for each type of mortality outcome including in-hospital mortality, 28d-30d mortality, and mortality in the ICU as shown in Table 2 in the main text. When comparing the results from different geographic regions, infection types, sample sizes, and years of publication, the stratified analysis and meta-regression were conducted in the studies reporting the same mortality outcome type as shown in Table S1-S7 in Supplementary Material Appendix 4.*

2- The literature search was conducted for articles published from 1994 to 2020, however the earlier

study published in this meta-analysis was from 2008. Didn't any of the studies published in the first 14 years of search met the inclusion criteria? Why was that? Authors could make a brief comment on that.

- *Response: We appreciate the reviewer's thoughtful comments. In the first paragraph of the results section, we have made a brief explanation on that that "Studies published before 2008 were not included in this meta-analysis because the early studies in this area focused primarily on reporting the outbreak of CRE infection or exploring its molecular characterization and epidemiology, as CRE isolation was first detected in the early 1990s. With the report of CRE isolation becoming increasingly frequent and arousing public health concerns, studies that compared mortality for patients with CRE and CSE increased and are included in this meta-analysis."*

3- In tables 2, 3 and 4 it would be useful to provide not only the number of studies included but also the number of patients in each subgroup.

- *Response: We appreciate the reviewer's helpful suggestion. We have provided the number of patients infected with CRE and CSE respectively for each subgroup in all tables in the revised manuscript.*

4- The authors mention on lines 22-25 that "Our study also has several limitations. Firstly, we only include two clinically important Enterobacteriaceae species, Klebsiella pneumoniae and Escherichia coli." The nine studies that included "Mixed Enterobacteriaceae pathogens" were also restricted to these two species? That was not very clear to me.

- *Response: We agree with the reviewer's comment and we are sorry for the unclearness of this sentence. This sentence is meant to illustrate that among the studies focusing on the specific pathogens in the Enterobacteriaceae family, we only included two clinical clinically important species. "The studies that included Mixed Enterobacteriaceae pathogens" refer to studies that reported the mortality outcomes regardless of the specific species of Enterobacteriaceae. To make it clearer, we have rephrased that sentence as "among studies focusing on specific pathogens, we only included studies that focused on two clinically important Enterobacteriaceae species, Klebsiella pneumoniae and Escherichia coli."*

5- On the discussion section, lines 17-23, authors mention that "to both high mortality rates in patients (61.1%) and CSE patients (51.7%) reported in only one study in Africa, which might be related to the low level of medical care and poor hygiene." Is there any objective evidence of low level of medical care and poor hygiene contributing to higher mortality in the setting this study took place? A reference should be added or the authors should explain better this hypothesis.

- *Response: Thanks for the reviewer's comment. According to the reviewer's first comment and suggestions, all the analysis was rearranged in the revised manuscript, the only one study conducted in Africa was categorized within the group of studies reporting ICU mortality and was analyzed in the meta-analysis. The result showed that the heterogeneity in studies from this group was very low. High mortality in ICU for both CRE and CSE patients is not only observed in the study conducted in Africa but also in other three studies, conducted in Europe. In the revised manuscript, the previous discussion about the study in Africa has been removed because the section of the discussion has been rearranged according to the new results.*

Response to Reviewer 2's Comments:

Reviewer 2: Comments to the Author:

This manuscript is very well written with clearly described study design, appropriate statistical analyses, and thorough interpretations of analysis results. The meta analysis presented in this manuscript provides valuable information to help understand the impact of carbapenem resistance on mortality in patients infected with Enterobacteriaceae, and its heterogeneity potentially contributed by factors such as economic status or geographic regions. The following are several minor comments that the authors may consider to incorporate in the revision of the manuscript.

1. The mortality outcomes adopted in the presented meta analysis take a variety of forms. The choice of the mortality outcome can potentially influence the rate of mortality reported in different studies. For example, 30-day mortality may tend to capture more cases of deaths as compared to 6-day mortality. It is worth some discussions on the potential limitation related to equally accounting for all kinds of measurements of mortality. Categorizing mortality measurements into a few groups and conducting analyses stratified by the mortality outcome type may help address the potential effect heterogeneity caused by this factor.

● *Response: We greatly appreciate the reviewer's insightful comments and suggestions have been taken to improve our manuscript. In the revised manuscript, we categorized the mortality measurements into eight different groups and conducted meta-analysis for each mortality outcome type as shown in Table 2 in the main text. Then, in the group that showed substantial heterogeneity, we further conducted stratified analysis for the groups of studies reporting in-hospital mortality, 28d-30d mortality, and mortality attributable to infection were analyzed in the stratified analysis as shown in Table S1-S3 in Supplementary Material Appendix 4. Similarly, these three groups were analyzed in the meta-regression except for the group reporting mortality attributable to infection because of insufficient studies for the meta-regression analysis as shown in Table S4- S7 in Supplementary Material Appendix 4.*

2. Page 10: I suggest including the interpretation of RR>1 (or 1) or RD>0 (or <0), in addition to the interpretation of RR of 1 and RR of 0.

● *Response: Thanks for the reviewer's thoughtful suggestion. We have included an interpretation in the section of "Data synthesis and analysis" as "When RR>1 or RD>0, it means carbapenem resistance has a positive effect on the risk of death for patients infected with Enterobacteriaceae; in other words, the risk of death from CRE infection is higher than that from CSE infection."*

3. Page10: I suggest changing the words "statistically significant" in "considered statistically significant when I^2 value >50% to words such as "high" or "substantial".

● *Response: We appreciate the reviewer's helpful suggestion. We have changed the word "statistically significant" to "substantial"*

4. The title of Figure 4 is not properly shown and needs to be fixed

● *Response: Thanks for the reviewer's careful review and comment. We have fixed the title of Figure 4.*

VERSION 2 – REVIEW

REVIEWER	Peng, Limin
	Emory University
REVIEW RETURNED	19-Nov-2021

GENERAL COMMENTS	The authors successfully addressed my previous comments.