Author’s response to reviews

Title: Fecal carriage and molecular epidemiology of carbapenem-resistant Enterobacteriaceae from outpatient children in Shanghai

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Author’s response to reviews:

Dear Prof. Robin L. Cassady-Cain,

Thank you for your letter. We have acknowledged your and the reviewers’ comments and constructive suggestions, which are valuable for improving the quality of our manuscript. Based on your helpful comments and request, we have revised the manuscript raised by the reviewers, and the amendments are made in the revised manuscript. Then some explanations regarding the revisions of our manuscript are as follows.

Review Comments to the Author from Prof. Benjamin Davido, M.D, M.S (Reviewer 1):

Major comment:

1. Those data can be of interest, but in the current version of this manuscript I don't see the point of this descriptive and monocentric study. Indeed there is no statistic performed and also no perspective in the current worldwide outbreak of CRE. Also we don't know if the study is retrospective (what I suppose).

Answer: Thank you for your kind suggestions. After we deeply think about this study, we consider this manuscript as a retrospective study which retrospectively describes the prevalence of CRE colonization in stool samples of outpatients in a tertiary pediatric hospital of Shanghai. Changes about this point have been made in revised version (Page 2, Line 6; Page 3, Line 26).
2. You will find below my suggestions to improve the manuscript. Thereafter I might consider it for publication.

Finally this manuscript need a total proofreading by a native english writer.

Answer: Thank you for your kind advice. The manuscript has been revised, and the English language was edited by a native English speaker from Edanz Editing. Changes have been made in the revised version.

Minor revision:

1. Page 2 in the abstract.

1) Line 9, precise Shangai (China).

Answer: Thank you for your kind suggestions. Correction has been made in the revised version (Page 2, Line 5).

2) Methods: Line 12: in a retrospective study?

Answer: Thank you for your kind suggestions. Correction has been made in the revised version (Page 2, Line 6).

3) Results: 3.6%, i do not agree with this finding i'll explain you why in the result section. (replace with 2.6%). Please add mean age and SD and number of children not of samples.

Answer: Thank you for your kind suggestions. We have deeply thought about your advice and have rechecked the medical records of these 9 children. Even though these 9 children had two risk factors of fecal carriage of CRE, we still do not know whether these CRE strains were acquired from hospital or not. We also suppose that these 9 children may bring the hospital acquired CRE to the community and caused the prevalence of CRE in community. Therefore, we think that these 9 children should be enrolled in this study and considered as outpatients though they had a medical past history of hospitalization. This may explain a phenomenon that the CRE colonized in fecal samples in community setting were likely to acquire from hospital.

The mean age and SD have been added in revised version (Page 2, Line 13).
4) Conclusion section of abstract: rewrite the conclusion by removing the last sentence with something such as "Such data must be confirmed over time with the screening of the close family considering the risk of transmission from and to adults.

Answer: Thank you for your kind suggestions. We have acknowledged that it may be incorrect to describe the conclusion. The last sentence in the conclusion section of abstract has been replace with “Such data must be confirmed over time with the screening of the close family considering the risk of transmission from and to adults” in the revised version (Page 2, Line 22-25).

2. Page 3:
1) Line 8: precise KPC1

Answer: Thank you for your kind suggestions. Correction has been added in the revised version (Page 3, Line 4).

2) Line 15 precise surveillance data in China

Answer: Thank you for your kind suggestions. Correction has been added in the revised version (Page 3, Line 8).

3) Line 19: when ? 2.9% in which year? same for 13.4%

Answer: Thank you for your kind suggestions. The rate of carbapenem resistant K. pneumoniae has increased from 2.9% in 2005 to 13.4% in 2014. Correction has been added in the revised version (Page 3, Line10-11).

4) In the methods precise the nature of the study ? retrospective ? prospective ?

Answer: Thank you for your kind suggestions. We all agree with your advice that this study is retrospectively conducted to understand the epidemiology of carbapenem resistant Enterobacteriaceae from fecal in children. Correction has been made in the revised version (Page 3, Line 26).

3. Page 5 results:
1) How many patients were included ? it's not clear is it 880 children ?
Thank you for your kind suggestions. In this study, one fecal sample was collected from one child and a total of 880 children were included. Correction has been added in the revised version (Page 5, Line 15).

2) Can you precise the mean age and SD please.

Answer: Thank you for your kind suggestions. The mean age of 880 enrolled children and CRE positive children was 1.1±2.2 years and 1.3±1.5 years, respectively. Correction has been made in the revised version (Page 5, Line 15 and 22).

3) Line 38: hard to consider those 9 children who had a medical past history of hospitalization as outpatients. I'll explain you why. First, what is the min and max duration between last admission? Some might have been admitted within the last month and considered as hospital-acquired fecal carriage. This is supported by the fact they had broad spectrum antibiotics recently which is already known as a risk of fecal carriage of CRE.

Answer: Thank you for your kind suggestions. We have acknowledged that those 9 children with CRE positive in fecal had a medical past history of hospitalization and the min and max duration between last admission was 3 days and 7 days, respectively. However, we have rechecked the medical records of these 9 children and find that no CRE clinical strains were isolated from other children in same department during the last admission. Even though these 9 children had two risk factors of fecal carriage of CRE, we still do not know whether these CRE strains were acquired from hospital or not. We also suppose that these 9 children may bring the hospital acquired CRE to the community and caused the prevalence of CRE in community. Therefore, we think that these 9 children should be enrolled in this study and considered as outpatients though they had a medical past history of hospitalization. This may explain a phenomenon that the CRE colonized in fecal samples in community setting were likely to acquire from hospital. Could it provide the explanation for this point? Thank you.

4) I suggest removing those 9 children, which makes 23 patients! 2.6%) which is around 3% so the same as your results and bring solid data.

Answer: Thank you for your kind suggestions. We have acknowledged that it may bring some controversy about those 9 children enrolled in this study. After we deeply think about it, we may think that those 9 children should be considered as outpatients though they had a medical past history of hospitalization. And this can explain a phenomenon that the CRE colonized in fecal samples in community setting were likely to acquire from hospital.
1) I will add after lines 11 the idea and data from this paper from Davido et al. "germs of thrones" from the ARIC recently published which showed the spontaneous decolonization after hospitalization (median of 49 days) this data support your idea from lines 5 to 11 about the carriage of your 9 children that are in fact hospital-acquired.

Answer: Thank you for your kind suggestions. We have acknowledged and agreed that those 9 children enrolled in this study might be in fact hospital-acquired. And it can explain a phenomenon that the CRE colonized in fecal samples in community setting were likely to acquire from hospital and carriages of these 9 children bring CRE from hospital setting to community setting. Also the mean day of hospitalization is about 4 days. Therefore we do not considered these children were not outpatients. Correction has been made in the revised version (Page 7, Line 9-12).

2) remove this paragraph which is useless from my point of view from line 16 to 24.

Answer: Thank you for your kind suggestions. Correction has been made in the revised version (Page 7, Line 16).

3) lines 44: add after this paragraph the idea that NDM1 are highly resistant pathogens with no effective beta-lactams, including recent ones such as ceftolozane tozabactam and ceftazidime avibactam. The only one that works are aztreonam. You can read and cite this paper https://www.ncbi.nlm.nih.gov/pubmed/28630191

Answer: Thank you for your kind suggestions. The idea about “NDM1 are highly resistant pathogens with no effective beta-lactams, including recent ones such as ceftolozane tozabactam and ceftazidime avibactam. The only one that works are aztreonam” has been added in discussion part. Correction has been made in the revised version (Page 7, Line 28 to 30 and Page 8, Line 1).

Page 8:

At the end of the discussion open the discussion with the interest of these findings considering the risk of transmission to and adults that travel and might give the carriage to other countries; Also we don't know if the described carriage of your children are not the result of an adult transmission. It is the main drawback of your study. I personally wanna know if the parents are
not carriers? We know that children are a burden for MDRO carriage and this question needs to be answered in another study.

Therefore, you need to change the conclusion, and it to this discussion point, once again by removing your last sentence and add the one I suggested in the abstract section.

Answer: Thank you for your kind suggestions. At the end of the discussion, we have added the opening discussion about these findings considering the risk of transmission.

Also we have changed the conclusion. Correction has been made in the revised version (Page 8, Line 19 to 30 and Page 9 Line 1-3).

Review Comments to the Author from Prof. Paul Lephart (Reviewer 2):

1. Overall, I believe the data presented here is interesting and provides a comprehensive picture of the scope of the diversity and spread of carbapenem-resistant Enterobacteriaceae in a pediatric outpatient population in an urban Chinese community. However, there are problems with English language usage throughout and the paper does not appear to have been proofread thoroughly as there are numerous typos as well. It is my opinion that the data presented makes this submission potentially interesting for publication but it is recommended that the complete manuscript including the revisions suggested below be internally reviewed by a native English speaker or manuscript review service prior to re-submission.

Answer: Thank you for your kind suggestions. The manuscript has been revised, and the English language was edited by a native English speaker from Edanz Editing. Changes have been made in the revised version.

2. Additional issues:

   1) Page 3, lines 29,35: References 7 and 8 appear to be incorrect and may be transposed. In addition, the sentence prior to [8] mentions "several studies" but only one is referenced...if there are truly several studies, reference them all.

Answer: Thank you for your kind suggestions. Sorry to make a mistake about the reference. Correction has been made in the revised version (Page 3, Line 16, 18)

   2) - Pg.3, Ln58: Define the transport medium used and how long and under what conditions specimens were stored prior to testing.
Answer: Thank you for your kind suggestions. Approximately 0.5 mg of stool or a rectal swab from each patient was stored in Cary-Blair transport medium (Hopebio, Qingdao, China) in 4°C condition up to 1 days prior to testing. Correction has been made in the revised version (Page 3 Line 29-30).

3) - Pg4, ln4: Why were only 1-5 colonies on a plate considered screen positive? What about plates with more than 5 colonies, why were these not considered screen positive?

Answer: Thank you for your kind suggestions. It may be incorrect to describe the screen positive result. After 24-48h incubation, at least one colonies per agar plate were considered as screening positive and further investigated. Correction has been made in the revised version (Page 4, Line 3-5).

4) - Pg5, ln38: What % of the non-CRE carrying population had prior hospitalization in the last 3 months and is this different that those that carried CRE. Same question for previous receipt of antibiotic therapy. Is there a difference between CRE carriers and non-carriers?

Answer: Thank you for your kind suggestions. We have acknowledged that we have made a mistake about the percentage rate of the non-CRE carrying population had prior hospitalization in the last 3 months and previous receipt of antibiotic therapy. And then we rechecked the outpatient medical records and found that only 38 children (4.5%, 38/848) had prior hospitalization and previous receipt of antibiotic therapy. Significant difference was observed between CRE carriers and non-carriers (Page 5, Line 25-27).

5) - Table 1: MIC50 and MIC90 values generally are not used unless there is a dataset of at least 100 unique MIC values. It is questionable how relevant these values are with such a small number of values.

Answer: Thank you for your kind suggestions. We feel sorry about the mistake made. The MIC50 and MIC90 values were removed from Table 1. Correction has been made in the Table 1 in the revised version (Page 15).

We hope that the revised version of the manuscript will meet the publication standard of BMC Infectious Diseases. We are looking forward to hearing from you soon.

Thank you and all the reviewers for the helpful advice.
Best wishes,

Sincerely yours,

Hong Zhang.

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