Author’s response to reviews

Title: Epidemiological characteristics, clinical manifestations, and treatment outcome of 139 pediatric Ebola patients treated at a Sierra Leone Ebola Treatment Center

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Manuscript Title:

Epidemiological characteristics, clinical manifestations, and treatment outcome of 139 paediatric Ebola patients treated at a Sierra Leone Ebola Treatment Center

Dear Editor of BMC Infectious Disease journal,

We would like to express our gratitude for further considering our manuscript for publication in your esteemed journal. We would also like to take this opportunity to thank the reviewers for taking their time to review our manuscript.

Please find below our point-by-point responses to the comments of the reviewers.

Editor Comments:
Response to Editor Comments:

Thank you for the support in improving our manuscript. The procedure has improved our work considerably.

Reviewer Reports:

Mahamoud Sama Cherif (Reviewer 1):

Reviewer 1, Comment 1: The manuscript entitled "Epidemiological characteristics, clinical manifestations, and treatment outcome of 139 pediatric Ebola patients treated at a Sierra Leone Ebola Treatment Center" is not providing any new insight into the literature. The authors declare that the selling point is the number of children affected with EVD in their analysis. This is because of insufficient review of literature about the topic. There are some publications with more cases than the one in this paper.

Response to Reviewer 1, Comment 1: Thank you Mr. Cherif for taking your time to review our manuscript. To the best of our knowledge and at the time of writing this manuscript our study involved the largest cohort of exclusively pediatric and Ebola Virus Disease (EVD) cases only to be investigated for their treatment outcome. Few large mixed cohort studies (mostly descriptive in methodology) involving both adults and pediatric EVD cases in the past investigated EVD cases for their Case Fatality Rates, as well as distribution of clinical signs and symptoms—see references: 1, 2, 5, 9, 10, 11, 12 and more recently Hartley et al, Levine et al. For those papers that investigated exclusive pediatric EVD cases their cohort samples were either small or they involved EVD comorbidity with malaria or belong to the age group 0 – 20 years of age: McElroy AK, et al 2000-2001 Gulu, Uganda investigated 55 exclusive pediatric EVD cases. Sha et al
2014-2016 Sierra Leone investigated 92 exclusive pediatric EVD cases. Smith M et al 2014-2016 Sierra Leone and Liberia 123 exclusive pediatric EVD cases but also involved EVD comorbidity malaria cases. Should the reviewer dispose of additional literature that we are not aware of that would contradict our response, we would be very grateful to receive such references in order to include them in our manuscript.

Because of these differences in the previous investigations of pediatric EVD cases we offer new as well as provide additional body of scientific knowledge to the treatment of pediatric EVD. Additionally the previous studies were mainly descriptive. Ours is both descriptive and a model investigation on the treatment outcome of EVD paediatric patient.

Reviewer 1, Comment 2: The CFR lower than what is reported in West Africa during the 2014 -2016 outbreak, seems to quite interesting because it may show how good was the pediatric case management at the 34 Military Hospital in Wilberforce, Sierra Leone between June 2014 to April 2015. The authors should provide a better understanding of the treatment protocol and their differences with other ETC’s in Sierra Leone.

Response to Reviewer 1, Comment 2: Indeed we also discovered our low CFR very interesting compared to other EVD treatment centers and have added some explanation on that in the Discussion section. Our study also included within the Method section (lines 173-181) the EVD treatment protocol used in 34 Military Hospital.

Reviewer 1, Comment 3: Line 294 -296: The reference of following statement "One mixed cohort study involving adult and 295 pediatric EVD cases reported a high CFR among young children and elderly EVD patients in 296 the 2014-2016 West African EVD outbreak. (34)" is not accurate.

Response to Reviewer 1, Comment 3: We thank Mr Cherif for identifying the incorrect reference. Correct citation has been inserted within manuscript (line 323-325).
Reviewer 1, Comment 4: None of the figure is attached to the manuscript

Response to Reviewer 1, Comment 4: We thank Mr Cherif for pointing out that apparently the figures were not available to the reviewing body. As per BMC Infectious Diseases journal submission guidelines figures should not be embedded within the manuscript but submitted as separate files. We hence did assume that the figures would be made available technically by the editorial procedure. The figures are uploaded. We ask the editors to assist on how the figures can be made available to the reviewers.

Reviewer 1, Comment 5: An interesting point that need to be explained is how the Education levels in children could make a difference in term of treatment outcome.

Response to Reviewer 1, Comment 5: Thank you for pointing out the need to explain how education levels in children may make difference in the treatment outcome. We have included such explanation within the Discussion section (lines 337-350).

Reviewer 1, Comment 6: No information about: time between onset and admission, exposure, viral load and follow up during the treatment.

Response to Reviewer 1, Comment 6: Although our medical records did capture date of admission and released, it however did not capture date of EVD onset as determine by the appearance of EVD signs and symptoms and hence we can’t determine the effect of treatment delay on EVD treatment outcome. Our medical data also did not capture EVD viral load of the patients. All these have now been included (lines 388 - 391) in the limitations of this study. We had earlier included in the manuscript the failure to follow up as a limitation in our study.

Reviewer 1, Comment 7: Line 182: The Sierra Leone Ethics and Scientific Review Committee (Opinion date 29 March 2917) is not accurate.
Response to Reviewer 1, Comment 7: The appropriate corrections have been made with the Declaration section (line 431) in the manuscript.

Reviewer 1, Comment 8: The conclusion of the study is not supported by the analysis done in this paper.

Response to reviewer 1, Comment 8: We appreciate you bringing to our attention the deficit in the Conclusion section which has now been edited. Our Conclusion (lines 404-408) now includes additional information from our Result section.

Hermans Veerle (Reviewer 2):

Reviewer 2, Comment 1: Dear author(s), first of all, thank you very much for discussing more on an important aspect of this devastating Ebola crisis, pediatric cases in Sierra Leone. It is very important that these findings are shared with the greater public so appropriate actions can be taken in next EVD outbreaks and settings (as in DRC at the moment) to make the response more appropriate towards paediatric patients as they are especially vulnerable.

I read the paper with great interest and hope my recommendations below can help to make the manuscript ready for publication. Please find below my detailed comments.

Response to Reviewer 2, Comment 1: We thank Mr Hermans Veerle for this supportive statement, and for his time and dedication to improve our work.
Reviewer 2, Comment 2: BACKGROUND, Line 61: It's rather Democratic Republic of the Congo

Response to Reviewer 2, Comment 2: Thank you for pointing out the above mistake. The sentence has been edited (line 59).

Reviewer 2, Comment 3: Line 62: the method of referencing is different, in line 61 you use 1-3, then in line 62 (1,4). Try to be consistent throughout the paper.

Response to Reviewer 2, Comment 3: We thank Mr Veerle for the remark. We believe that we have incorporated a correct referencing technique, in which consecutive series of reference numbers are indicated by hyphen, while non-consecutive series are indicated and separated by commas. (1-3 implies reference 1, 2 and 3 while in Line 62; 1,4 implies reference 1 and 4 only).

Reviewer 2, Comment 4: Line 67: why specify only bats, chimpanzees and gorillas? It is expected that bush meat in general can carry the virus. The bats are considered the vector but other animals such as chimpanzees and gorillas, but also antelopes, forest pigs etc might be infectious when eating and/or processing meat.

Response to Reviewer 2, Comment 4: The sentence has been edited accordingly in line 65.

Reviewer 2, Comment 5: Line 79-124: It's a good overview of what is known in the literature, but it seems too long and jumping from CFRs from Uganda back to West Africa and in all age categories. Can this be rewritten in a more structural way? What would you need for this article, what is important to make your point with your research? If the limitations are mainly the small sample sizes, then highlight this as in your research this is a big asset.
Response to Reviewer 2, Comment 5: We have made some adjustments in the Introduction section (lines 129-140) to guide the reader in a better way to the objectives of our study.

Reviewer 2, Comment 6: Line 125: There are several experimental treatments ongoing in the current outbreak in Eastern DRC + ring vaccination ongoing. You might want to add this in your background and reference to it (a lot of information on WHO website).

Response to reviewer 2, Comment 6: The respective sentence in lines 125-128 has been edited to include several experimental treatments.

Reviewer 2, Comment 7: Line 134: "using a large data set"

Response to Reviewer 2, Comment 7: The respective sentence has been edited (line 135).

Reviewer 2, Comment 8: Line 135: I miss a bit the operational reason why this retrospective analysis would give added value to future outbreaks. What can be implemented using your results? Is it the aim to change case definitions, then definitely mention it here already.

Response to Reviewer 2, Comment 8: Thank you for highlighting the need for the inclusion of the justification of our study. Accordingly, a sentence justifying the objectives (lines 138 - 140) of this study has now been included.

Reviewer 2, Comment 9: METHODS. Line 152: typo "Stage one EVD is, also known as the dry or early phase, is characterized"
Response to Reviewer 2, Comment 9: The sentence (line 154-155) has been edited.

Reviewer 2, Comment 10: Line 153: same for Stage two

Response to Reviewer 2, Comment 10: The sentence (line 155-156) has been edited.

Reviewer 2, Comment 11: Line 157: specify where Lakkah exactly is situated

Response to Reviewer 2, Comment 11: The sentence (line 160) has been edited.

Reviewer 2, Comment 12: Line 162: where routine malaria RDTs performed on paediatric patients? Might be interesting to mention if a treatment was given anyway.

Response to Reviewer 2, Comment 12: No malaria RDT or other means of malaria diagnostics was performed. However the treatment protocol included anti-malaria medications for each patient (Line 173 - 177).

Reviewer 2, Comment 13: Line 167: you jump immediately to ethics review but I miss a section on setting: general and specific. A bit more information on Sierra Leone, Freetown (health structures, how were the referrals done in the outbreak, where there any other ETCs + more information about the military hospital, who was in charge, how many staff, how many beds, capacity, etc)
Response to Reviewer 2, Comment 13: A paragraph on Sierra Leone, its health system referrals, 34 Military ETCs and staffings has been added in lines 162 - 171.

Reviewer 2, Comment 14: Line 187: who anonymized the data? Was this done by the researchers and how was secure storage of the data ensured?

Response to Reviewer 2, Comment 14: We have included a statement about who anonymized the data as well the security regarding the stored data in lines 205 - 208.

Reviewer 2, Comment 15: Line 264: typo "There were differences in the likelihood of a pediatric EVD patient will dying ie during EVD treatment as a result of gender difference"

Response to Reviewer 2, Comment 15: Thank you for bringing to our attention of this typo. We have corrected the sentence (lines 290 - 293).

Reviewer 2, Comment 16: DISCUSSION. You mention in the results (line 229) a significant difference in educational background of children and CFR. This doesn't come back in the discussion. What does it mean?

Response to Reviewer 2, Comment 16: A discussion on the significant difference in educational background of children and CFR has been added in the Discussion section (lines 337 – 350).

Reviewer 2, Comment 17: Line 288: male instead of men
Response to Reviewer 2, Comment 17: The sentence has been edited (line 404 – 408).

Reviewer 2, Comment 18: Line 295: it can indeed be expected that CFRs for very young and older patients are higher, as shown in different studies already. But always interesting to mention why (as you did for the difference in gender)

Response to Reviewer 2, Comment 18: An explanatory sentence (lines 328-331) has been added.

Reviewer 2, Comment 19: Line 297: I wouldn't use too much statistics and numbers in the discussion, it doesn't read very well and it's clearer if you make a general comparison with your study, not exact numbers because the methodology and case definitions might be different anyway

Response to Reviewer 2, Comment 19: The Discussion Section has been edited with most statistics that were already stated in the Result section removed.

Reviewer 2, Comment 20: Line 310: again, this is repetition of the results.

Response to Reviewer 2, Comment 20: This repetitive sentence has been removed.

Reviewer 2, Comment 21: ACKNOWLEDGEMENTS. Line 410: always nice to mention the patients who suffered the most during this horrendous outbreak.
Response to Reviewer 2, Comment 21: We agree completely with this remark. This sentence has been edited in line 461 to acknowledge the individuals who suffered during the EVD outbreak in Sierra Leone.

Reviewer 2, Comment 22: REFERENCES. Differences in fonts and editing make sure it is consistent for all references

Response to Reviewer 2, Comment 22: We have now ensured that the fonts, font size and editing for all references are consistent (lines 468 – 569).

Reviewer 2, Comment 23: TABLES AND FIGURES. Possible to have one of the tables as a figure? It reads better than a long table with numbers.

Response to Reviewer 2, Comment 23: We agree that figures can have advantages by allowing readers to get a more rapid grasp of data. However, we would argue that the concrete data and the comparison thereof is of advantage in this case, and would suggest to rather keep the data presentation here as a table.

Reviewer 2, Comment 24: Table 1: title - add location, time, repeat what 'pediatric' means (a table needs to be able to stand alone)

Response to Reviewer 2, Comment 24: We have edited the title in Table 1 accordingly (line 578 -580).

Reviewer 2, Comment 25: Table 2: idem - add location, time
Response to Reviewer 2, Comment 25: We have edited the title in Table 2 (line 585 -587)

Reviewer 2, Comment 26: Table 3: idem (+ error in repetition of the title)

Response to Reviewer 2, Comment 26: We have edited the title in Table 3 (line 591 - 594)

Reviewer 2, Comment 27: Figures: I couldn't see the figures in this document? But always good to have a map, however, are the other ETCs in the area presented as well?

Response to Reviewer 2, Comment 27: There are figures (including a map of Sierra Leone) to this manuscript but they are saved as a separate file in line with BMC journal requirements. If figure files were not available to the reviewers, we would like to ask assistance by the editors.

We would like to express our thanks once more to the reviewers for their thorough assessment of our manuscript. We are convinced that their recommendations have improved the quality of our manuscript substantially.

With best regards, and on behalf of my co-authoring colleagues,

Jia Kangbai