Author's response to reviews

Title: Ebola haemorrhagic fever outbreak in Masindi District, Uganda: outbreak description and lessons learned

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Author's response to reviews: see over
Heidelberg, 10 Jul. 11

Dear Dr Marshall,

Referring to my email dated 16 May I would like to express our thanks for your willingness to consider publishing our paper as Correspondence article. We are happy with that editorial decision.

We have addressed the reviewers’ comments below, most of the time accepting their suggestions. Where we disagree with a suggestion, we have explained why.

On ethics approval we have inserted the following paragraph in the text: “No ethics approval was considered necessary, since we used routine data collected routinely in an emergency situation. Patients, relatives and health care workers were informed that a report would be published, and that their privacy would be respected. Permission to use the data for publication was granted by the Ministry of Health, whose local representatives at the time are among the co-authors of this paper.”

All revisions in the manuscript have been highlighted as ‘track changes’.

Looking forward to receiving your response,

With best regards,

Matthias Borchert

Reviewer: Amy L Hartman

Reviewer's report:

This is a well-written descriptive manuscript describing the epidemiological course of a specific part of the 2000 Ebola Sudan outbreak in Uganda. The paper focuses on the part of the outbreak that occurred in the Masindi District. The report covers the epidemiology of the outbreak, including specific narrative details on the response effort by various parties. This report is a really useful description of the outbreak with a focus on what responses worked and what failed, including recommendations for future outbreaks. I believe this report is important to the scientific community. In many previous Ebola outbreaks, the details of the outbreak and subsequent response have not been well-documented, and it is difficult to learn from the experience to benefit future outbreaks. This manuscript contributes to our knowledge of specific outbreak responses to deadly hemorrhagic fever outbreaks in resource-poor settings.

Discretionary Revisions:

1. In general, the figure legends need more detail. Provide additional descriptive detail in each figure legend to describe the intent of the figure. For example, Figure 3’s legend reads simply “EHF outbreak, Masindi District, Uganda, 2000.” Include additional information such as “Graph shows the number of laboratory confirmed
Ebola cases over the course of the outbreak. Fatal and non-fatal cases are indicated.” That is just an example.

Details have been added to the figure legends as follows:

Fig 1: The map shows the location of the epicentrum (Gulu) of the EHF outbreak in Uganda, 2000, and of the locations were satellite outbreaks occurred (Masindi, Mbarara).

Fig 2: The Ebola ward in Masindi corresponds to the typical set-up of FHF isolation wards consisting of three separate compartments: low risk for staff, storage; high risk for probable cases; high risk for confirmed cases; decontamination stations between compartments.

Fig 3: The graph shows the number of laboratory confirmed Ebola cases over the course of the outbreak. Fatal and non-fatal cases are indicated.

Fig 4: The graph shows the schematic spread of EBOV from the epicentre in Gulu to Masindi district, within the index family (five epidemiological gernations of cases), to health workers before and after the introduction of barrier nursing, and into the general population. Sex of the case and outcome of the disease are indicated.

Fig 5: The schematic map shows the locations of the index family’s homesteads, with footpaths connecting them, and approximate distances between them. Fatal and survived cases are indicated. No cases occurred in homesteads not belonging to the index family.

Fig 6: The graph shows the three genealogical generations of the index family, indicating sex, EBOV infection and EHF outcome. Attack rates per generation and in total are presented.

Fig 7: The graph shows hospitalised survived and fatal EHF cases from the community and among health workers, with date of admission and date of discharge/death, before and after the reinforcement of the outbreak response team.

2. Table 2: There is a lot of data in this table and it is a bit confusing to interpret. Is there a better, clearer way to present the data?

   It is true that the table provides a lot of detail. We believe that the value of this table is in its detail, which is likely to be relevant for the community of responders to FHF outbreaks. We did not find a clearer way to present the data, and since the other reviewers did not comment on the table, we left it unchanged.

3. Table 3: format of the table is not clear; please revise to a better format. It is also not clear exactly what the statistics are referring to (i.e. which groups are being compared in the statistical tests – this information can possibly be included in a more descriptive figure legent)

   The formatting has been thoroughly revised, and it has been clarified in the legend what the tests compare.
4. For figure 5, on the figure itself, please differentiate the actual legend on the figure from the rest of the figure by a box or other demarcation. As it is, it is difficult to tell the figure from the legend. Provide and explanation of the arrow (Kaduku Trading Centre) and lines connecting the houses. Do these represent streets or walking paths?

The legend is now surrounded by a box. The arrow is explained as pointing to Kaduku Trading Centre in a distance of about 3 km. Lines connecting the houses are identified as footpaths in the legend.

Reviewer: Sadegh Chinikar
Reviewer's report:
it is OK
Thanks.

Reviewer: Francesco Maria Fusco
Reviewer's report:
Major Compulsory Revisions:
1- Add the study design in the title: “Ebola Hemorrhagic Fever in Masindi district, Uganda: description of an outbreak”

The title has been changed as suggested. Since we feel that the paper goes beyond describing the outbreak we have opted for “Ebola haemorrhagic fever outbreak in Masindi District, Uganda: outbreak description and lessons learned”

2- In the abstract, methods are not well described. You should refer to the article methods only, and not to the outbreak management methods. Who led the outbreak response in Uganda is a wrong and unuseful information, here. The last sentence of the paragraph is ok. Try to enlarge it, adding some part on statistical analysis, or simply delete the first part

We have revised the abstract as suggested.

3- Please clearly write your objective at the end of introduction section. You only say “This paper focuses on...”. It is not sufficient. You should identify the study design and the objectives. You may move here the section “Objectives of the study”, which is currently in the methods, without the final sentence on statistical analysis.

The section “Objectives of the study” has been moved (without the heading) to the end of the introduction section, as suggested. We have agreed with the editor that the paper does not report on standard research, and therefore we do not specify a study design.

4- The section “Methods” should be substantially revised. Indeed, in your version, methods and results are mixed. In general, the most of required “methods” data are included, but also many results are included in this section. In general, you do some confusion between the article methods (study design, setting, description of study
population, observation period, case definitions used, data collection methods, diagnostic methods, and statistical analysis) that should be included here, and outbreak management methods (co-ordination of the response, active surveillance, case management and public mobilization, using your titles), that should be moved in the results. Please refer to STROBE guidelines, in order to re-organize your methods section appropriately.

Revised as suggested: the description of the response has been moved to the results section, and sub-sections have been re-arranged.

5- Some more specific comments about methods, not considering if these parts should be moved elsewhere or not:

a. In the paragraph “method, outbreak response, coordination”, lines 7-10. Daily meeting also have some human and time costs: they are time consuming, and deflect from other duties and activities. Please address with a brief comment this problem.

Meetings in general certainly bear the risk of being a waste of time. However, in the way they have been conducted in Masindi, they were time well invested – without the frequent information exchange and the face-to-face contact, fostering trust and confidence, the heterogeneous response team would have risked falling apart. We have added the following sentence to the discussion section: “The daily meetings of the District Task Force’s technical committee, although time-consuming, played a crucial role in ensuring that all response aspects were covered while avoiding the duplication of efforts, and in fostering mutual trust and confidence among intervening partners of various backgrounds.”

b. In the paragraph “active surveillance” it is not clear how the alerts arrive to the mobile teams. Given that the confirmed outbreak is limited within a limited area and within the “index family”, on what it is based the active surveillance of other possible cases? You said that alerts were recorded in a “rumour registry”, and these alerts were responded to mobile surveillance teams: which is the origin of the rumors? Who collected them?

We only know in hindsight that the outbreak was limited to the index family; at the time it was feared that transmission chains of unknown origin existed in Masindi like in the epicentre Gulu. The procedure has been clarified by adding “Members of the public reported alert cases to the nearest health facility or the local government representative, who forwarded the alert to the District Health Office.”

c. In the paragraph “case management”, in the part about PPE, please clarify if a defined sequence for donning and removal of PPE is suggested. Remember that, during outbreaks of Highly Infectious Diseases such as Ebola and SARS, not appropriate removal of contaminated PPE has been suggested to be linked with disease transmission to HCWs.

Clarified by revising the sentence to “Hospital staff wore personal protective equipment (PPE) when caring for suspect, probable or confirmed cases; there was a strictly defined sequence of donning and removal of PPE according to WHO guidelines”
6- In the section “Results. Performance of surveillance activities” you did an interesting discussion about the efficiency of your case definitions. This discussion is partially impaired by a limit: these case definitions, at least in Masindi, were not tested in a real epidemic situation. In facts, all detected cases have been identified within the index family. This situation surely contribute to make case finding efficacious, because it brings to a better awareness of physicians and researchers for suggestive symptoms. Please clearly declare this limit and add a sentence about this peculiar situation.

The following sentence was added to reflect this limitation “One has to bear in mind, though, that most cases came from one extended family, so that health workers using the case definition on its members had the benefit of an increased prior probability, which likely made the case definition more efficacious than in an outbreak with many transmission chains of unknown origin.”

7- In the same section, you also speak about reasons for delay in hospitalization. You said that extreme delays occurred among HCWs only, and not among index family members. Then you said that causes for prolonged delays included (1) missed daily visits by the surveillance teams, (2) insufficient transport capacity, and (3) lack of cooperation by the individuals being followed-up, i.e. refusal to report symptoms or be taken to the hospital, as a result of fear or mistrust of the response team. These reasons seems to be applicable to community cases (especially the reasons 1 and 3), while it is hard to imagine these reasons for HCWs, that should not been included in daily visits, and should not be affected by mistrust of the response team. Please clarify this apparent contradiction.

The only reasons which applied to health worker cases were fear and mistrust indeed. We have clarified as follows: “Only 37% (13/35) of patients were assessed on the day of onset or the next day as it would have been appropriate; 40% (14/35) were hospitalised on the 2nd day after onset, which may be considered acceptable, but for 23% (8/35) the delay was prolonged (≥3 days). Extreme delays (5 to 8 days) occurred in 3/13 HW cases (23%), but did not occur in community cases (p=0.044, two-sided Fisher’s exact test). Causes for prolonged delays between onset and clinical assessment included, in community cases, missed daily visits by the surveillance teams and insufficient transport capacity, and, in both community and health worker cases, lack of cooperation by the individuals being followed-up, i.e. refusal to report symptoms or be taken to the hospital, as a result of fear or mistrust of the response team.”

8- Section “Challenges in the health system”, last sentence. Sorry, but I didn’t understand this sentence. Please rephrase it.

The sentence now reads “This problem can be solved by using written communication by email, transmitted via telephone landlines, mobile phone networks, satellite connection or high frequency radio.”

9- Table 2. Please clarify which is the origin of data about symptoms. You said that clinical records have been lost, or destroyed. So, how can you have such detailed data?
The only clinical data we have are data collected by the surveillance teams prior to admission. Clarified in the methods section: “While some clinical data could be extracted from surveillance records, clinical dossiers of individual patients were not available for analysis.”

Minor Essential Revisions

1- Abstract, result paragraph, last sentence: I suppose it is “at the beginning”, and not “and the beginning”
   Corrected.

2- Abstract, conclusion. You use the acronym HWs for the first time, please develop it. Moreover, why do not you use HCWs (health-care workers)?, which is widely used, and more easy to understand by readers? If you prefer to use HWs for some specific reason, please explain me (not in the article, but on separate comments)
   We have no preference for HWs over HCWs and have changed to HCWs

3- In the section “Results. Course of the epidemic”, 4th paragraph, line 3, please move (n=23) at the beginning of the sentence, just after “All”.
   Revised, but differently than suggested. The sentence now reads “All except the first three cases (n=23) were treated in the Ebola ward of Masindi Hospital”. For “All cases”, n would be 26.

4- Section “Results. Case fatality”, first paragraph, line 5. Please delete the first (or the second) “were”
   Corrected.

5- In the section “conclusion”, the last paragraph is not useful, according to me. This article is not focused on medical management of Ebola cases, such a conclusion about therapeutic approach and supportive therapy is misleading.
   We beg to disagree. We strongly feel that it is no longer acceptable to respond to FHF outbreaks without documenting how FHF patients have been treated, and to which avail – so we are calling for standards on clinical documentation in the context of such outbreaks. The fact that some anecdotal evidence suggests that pro-active supportive treatment might be beneficial only underlines the importance of proper documentation.

6- Table 3. Why did you report some p only? Please report all, or only significant ones.
   We report the overall p-value for a difference in proportions, and the p-value for a difference in means. No other p-values have been computed, given the small number of observations. We have clarified by revising layout and legend.

7- Figure 2. This figure is unclear for me. Which are the doors? Is there a way-in and way-out pathways? Please modify it.
   The figure has been modified to indicate doors, one-way and two-way pathways.
Discretionary Revisions: the article is interesting, but very long. Try to shorten it as more as possible. Another general, personal comment, that is the most important. You had the unique opportunity to observe an Ebola outbreak in a sort of “semi-experimental” situation: limited population, no contacts with other persons, limited environment. I think that specific data about social and cultural behaviors more at risk for Ebola transmission could be very interesting. You only said that giving care to sick persons, and having food together were linked with transmission, but you did not sufficiently develop this point. Did you identify some specific risk behavior? Such as taking food from the same plat, or kissing, or sleeping together, or some other everyday activities, or cultural-specific actions? If yes, please add a discussion about these points in the article, it may add a great interest to the article.

We have shortened the manuscript while preserving the details which constitute the value of the paper.

It is true that the Masindi outbreak were happened in a sort of controlled setting and provided a rare opportunity to study an EHF outbreak. But we were, at the same time, very limited in the time and effort we could invest in research, since all of us who were in the field were in charge of controlling the outbreak. We could therefore only collect anecdotal data on risk behaviour within the index family, but not conduct a proper epidemiological study. Nevertheless we have elaborated the issue in the following way: “During times of crisis, the local tradition required that members of the index family stay even more closely together than they do anyway, taking food from the same plates, and sleeping close to each other in the same few huts at the centre of the compound rather than living scattered over an area of approximately 4 hectares as in normal times” (Error! Reference source not found.).”

Reviewer: Vincent Munster

Reviewer's report:

Dear editor,

I have reviewed the manuscript entitled “Ebola haemorrhagic fever outbreak in Masindi district, Uganda” by Borchert and co-authors. The manuscript offers a largely descriptive report of the outbreak of SEBOV in the Masindi district in Uganda. Although largely descriptive, the manuscript does have it merits and is an important contribution to the existing literature. However, the manuscript in its present form seems overly long and could use some streamlining.

We have made an effort to shorten and streamline the paper.

Minor points:

Line 135, please incude references to the methodologies used throughout the outbreak to detect infected cases (either PCR or Elisa).

References have been inserted

Line 138 “temporary CDC biosafety level 4 facility”, technically the field settings used in outbreaks do not qualify as level 4 facility, the in line 363used term field laboratory would be more appropriate.
Revised as suggested.

Line 184, “oral dehydration”, should be rehydration.
Corrected.

Line 252 “epidemiological criteria” are these the same as used in table 1?
Yes. The reference to Table 1 is now made in the text: “Fifty-two suspect cases (Error! Reference source not found.) were identified by surveillance teams. Eight were deceased; two of these were subsequently classified as probable cases by epidemiological criteria.”

Line 332 “alert case definition”, refer to table 1.
Revised as suggested.

Line 412 “International ….enforce” this statement should have a reference.
The statement is not based on the published literature, but on our own experiences as FHF outbreak responders and the discussions we have had with our colleagues. Modified to “In our experience, international experts are usually reluctant to recommend quarantine measures, being concerned by human rights issues, fearing to antagonise the quarantined community, and arguing that quarantine is difficult to enforce.”

Line 630 “On the other …. False” this line need references to the exact PCR protocol used.
We agree that it would be useful to specify the exact protocol which was used during the outbreak, but this information is not available to us. We do not think that this information is essential, though, since we are commenting here on the consequences of false positive PCR results, not on the reasons for false positive results.

Figure 5, I do not feel that this figure adds much to the manuscript and could be deleted.
Since this view was not shared by the other reviewers (one of them gave detailed instructions how to improve the figure so presumably felt it to be important) we opted for leaving it in.