Author’s response to reviews

Title: Mortality after Inpatient Treatment for Diarrhea in Children: a Cohort Study

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Author’s response to reviews:


Reviewer #1:

General comments: Thank you very much for considering me as one of the reviewers of this manuscript. The topic is important and the list of authors is highly experienced in this field. Moreover, the manuscript is written with a logical flow and really reader friendly. The authors should be congratulated for that. On the other hand, although, the topic is very important, most of the observations were known and the new observation is few. This may be considered for the acceptance as a brief report/short communication. Thus, the respected authors should revise this as brief report/short communication and submit for the acceptance.
Specific comments: The authors concluded in the 2nd sentence of abstract (and some part in the text) as "ensure referral to and facilitate uptake of services for malnutrition and HIV, and advise parents to seek help early in case of further problems." No results related to the statement are shown and thus, this sentence does not support results of the study. At best the authors can say (both in abstract and text) that "the results may accentuate the importance of referral ---------"

- Thank you. We have amended the abstract to state that further research is needed on retention and outcomes of HIV and malnutrition clinic services in this context.

Reviewer #2:

Overall comments: This is an interesting study which deserves to be published. The authors have conducted a comprehensive study and analysis. A few minor revisions are required (see below), especially - In the conclusion (of the abstract) and the first sentence of the discussion, avoid making over-generalisations from this data on the effect of diarrhoea on post-discharge mortality. This was only analysed in a subset which is not representative of the general population. Although this is acknowledged in the small print of the discussion, the headline conclusion is misleading.

- As also suggested by reviewer#3, we have altered the analysis to only include the KHDSS residents and amended the abstract to explain that our findings were for children resident within the KHDSS.

- The discussion would benefit from a slightly deeper consideration of implications for policy and clinical practice. As the authors state, the risk factors for inpatient death are probably already well recognised and so this may not change practice. However risk factors for post-discharge deaths are probably less widely known. Children who have malnutrition and HIV should be being followed up. However to what extent is this practice being implemented? Is further research needed on barriers to implementation of this policy (this is probably both on the patient
and on the provider side). Also, should new follow-up procedures be trialled for patients who have had prior admissions, as these were at greater risk?

As per the response to reviewer #1, we have included a section in both the abstract and discussion on retention and outcomes in HIV and malnutrition services, and included a reference about rates of loss to follow-up in sub-Saharan Africa HIV clinic settings.

Specific minor comments and corrections:

Intro: ".. since that review (up to end of May 2018), 17 additional studies reporting outcomes of treatment of children with diarrhea in low and middle income countries have been published." - I find it hard to believe that 17 studies have been published on this subject in the last 3 months?? Please check date. Was it really May 2018?

-We have changed the wording in the introduction section to show that Wiens’ review included papers up to October 2012 and that 17 papers were found in the new search from then up to May 2018.

Results: line 181-182: "Signs of some dehydration and severe dehydration were present in 1,117 (24%) and 1,611 (35%) children respectively" - please check - is this the right way round? I would expect "severe dehydration" to be a subset of "some dehydration". Or are these 2 separate categories? Please clarify.

-The categories are exclusive – we have specified this in the definitions section of the methods.

Table 1: categories of temperature do not make sense. 36-39 encompasses both afebrile and febrile children. I would recommend a standard cut-off - for example 37.5°C.

-We redid the analysis using more conventional cutoffs of afebrile to 36-37.5°C and febrile to >37.5°C as suggested.
What is meant by "temperature gradient"?

-We have explained this in the methods section

Please add a section to show primary discharge diagnoses for the children in each group.

-We have put this information in supplementary table 1

We also need a table showing primary cause of death, both in those who died as inpatients, and post-discharge.

-This is now in supplementary table 1. We don’t have data on cause of death post-discharge.

Discussion sentence 1:

"Among children admitted to hospital, diarrhea was associated with increased inpatient mortality, but not post-discharge mortality." - this needs to be qualified by saying it is not possible to comment overall, but only for children resident within the DHSS. As risk of inpatient death was much higher in children resident outside the DHSS one might presume that the same is true for risk of post-discharge death. It is likely that children resident in the DHSS are not representative of the general population because (a) they live closer to the hospital and (b) in general there are more interventions and better follow-up in a DHSS than outside it. You do point out at the end of the paragraph that those living outside the DHSS are likely to have higher post-discharge mortality - so the first sentence needs to be re-written to avoid over-generalising your results.

-We have removed non-KHDSS children from the inpatient mortality analysis and have reworded the beginning of the abstract and discussion to highlight that our findings are for the KHDSS children only.

Discussion line 262: "children admitted with SAM and HIV infection are linked to outpatient
management of these conditions upon discharge." - is there any measure of uptake or compliance with follow-up? I would imagine this would be less in those outside the DHSS?

-We do not have data on compliance for this cohort.

Figures are missing titles.

- The titles are in the main manuscript as per author instructions from BMC Medicine.

Reviewer #3:

This study examined post-discharge mortality among children who were admitted with diarrhea from a single hospital in Kilifi, Kenya. This is an important study in an area of pediatric global health, and one that has received relatively little attention over the past several decades. Despite an excellent rational, what appears to be high quality data and a strong methodology, I have several comments that may improve the overall quality of this manuscript.

Intro: Overall, the introduction reads well and makes a logical argument to justify the study. There is a claim that diarrhea is "reported to be associated with increased risk of post-discharge mortality in several settings in resource poor countries". This is not referenced.

- The Kenya (Snow) and the urban and rural Bangladesh papers (Stanton and Roy) are now referenced for this sentence.

Increased compared to what group? Perhaps the relevant reference can be added in here.
-The Snow paper compares them to children in the community who were not admitted to hospital, we have added the reference.

This is important since the results of this study show diarrhea not to be associated with an increase in risk compared to a "reference" population of hospitalized children. The SLR that is referenced mentions 3 studies, reporting only 1 study which shows diarrhea as a risk factors for post-discharge mortality (compared to malaria).

The introduction also states that "This review also identified 5 papers examining diarrhea as one of several risk factors for mortality after general pediatric admissions: 3 from Kenya, one from Guinea Bissau and one from Uganda.[1, 2, 9-11]" I'm not sure I'm following this exactly. Reference 1 is not included in the review, but does address diarrhea as a risk factor. Reference 11 is not a study on post discharge mortality. Of reference 2, 9 and 10, only reference 10 shows diarrhea as a risk factor (but in this case compared to Malaria). There is no study from Uganda showing diarrhea as a risk factor

-We apologize for this mistake and appreciate that the author of the review was one of our reviewers! We have made changes to the introduction discussion about previous papers on post-discharge mortality.

Methods: This study is examining first and foremost post-discharge mortality. All analyses of this outcome include only the KHDSS population. Why then do you even include the non-KHDSS children in this analysis?

-We originally included all diarrhea children in the inpatient mortality analysis for generalizability and to improve the statistical power. We have removed non-KHDSS patients from the inpatient mortality analysis to improve the flow of the paper.

This study almost reads like it was designed as a prospective cohort, yet it appears to have been a retrospective cohort analysis, using what appears to be routinely collected clinical data, linked to a community surveillance program. Perhaps more clarity can be provided as to what exactly subjects were consented for and how this particular analysis fits into the broad Kilifi Surveillance program. How was quality assured?
We have specified that it was a retrospective analysis of a cohort where data were collected systematically and entered into a database in real time, effectively prospective surveillance which is later extracted for a variety of studies. Inpatient treatment followed national guidelines. KHDSS data came from the 4 monthly census rounds and missing outcome data were not included in the analysis.

It is clear that non-KHDSS subjects fared much worse than KHDSS subjects (nearly double in-hospital mortality). Since all the post-discharge outcomes are in the KHDSS populations it thus makes sense to keep this population the focus of both pre and post-discharge analyses (including non-diarrhea comparisons).

We agree with your recommendation and have removed the non-KHDSS children.

Does it not make sense to compare diarrhea as a risk factor against other sensible disease groups, rather than a mix of all other subjects who did not have diarrhea? Since this is meant to inform practice and research in other areas, many of which have different underlying populations (i.e. different prevalence of other illnesses), I think that the authors should consider categorizing the non-diarrhea admissions for the purposes of comparison.

We have added analysis of pneumonia, which is the other large group of admissions, including overlapping children who had both diarrhea and pneumonia, and children with neither of these. Analyzing more subgroups would require larger numbers of post-discharge deaths.

Several continuous variables were analysed as a dichotomous variable (like SpO2, Temperature, RR, HR, etc.). I think that perhaps it may make sense to utilize all the available data by analyzing these as continuous variables (age adjusted if necessary). For the variable of hypoxemia, for example, there were only 2 cases (in the post-discharge analysis), but if measured continually, this will increase the power of this analysis.

This is difficult to justify from a clinical point of view for some variables as extremes at both ends of temperature, respiratory rate, heart rate etc are high risk (i.e. non-linear or with thresholds). Linear analysis of continuous variables works for low MUAC and HAZ.
Results: With the stark effect of KHDSS status on in-hospital outcomes, it really does not appear to make sense to include the non-KHDSS group in this analysis given the lack of post-discharge information (which is the ultimate purpose of this paper). It is possible that being a resident of the KHDSS population may have an interacting factor on other variables, making the entire in-hospital analysis difficult to interpret when these groups are combined, as they are. While it does add numbers, and statistical power, it also makes this paper a little more confusing to read and interpret.

-We now only include KHDSS residents in the analysis.

Is the location of death available in this dataset? Several studies have shown that most post-discharge deaths occur outside of health facilities/hospitals and it would be interesting to see this data presented here if it is available.

-We have indicated if post-discharge deaths were known to have occurred in our hospital or not in the text of the results section. We don’t know if any children died in other hospitals.

As mentioned earlier, the comparison of diarrhea vs no diarrhea may not be the most ideal comparison. Consider have diseases specific comparisons. Related to this, Table 1 contains no data on diagnoses (other than HIV and malaria testing). Is this data available? What about co-morbidities?

-We have included comparisons with pneumonia, as above.

The statement that post-discharge mortality was associated with SAM, but not MAM, is perhaps a little misleading. Categorizing children as SAM or MAM automatically reduces the analytic power of the analysis of anthropometry, compared to utilizing continuous data. In fact, in the multivariate model, MUAC, as a continuous variable, was highly significant. This suggests a continuum of increasing risk as MUAC decreases. While I have no objection of the supplemental table, perhaps focusing on the primary results (i.e. those reporting MUAC) is ideal.

-We have removed mentions of SAM and MAM on page 12 of results.
This study developed a predictive model for assessing risk for post-discharge mortality among children admitted with diarrhea. It would be helpful to include the regression equation for this model so that others can utilize this work from a validation perspective.

- We have now included these equations as supplementary information.

Discussion: When was the rotavirus vaccine introduced in the Kilifi area?

- In July 2014, this is added to the text.

The concluding paragraph included the statement about SAM, but it was MUAC that was included in the main multivariable analysis, so consider rewording to include MUAC

- We have now included low MUAC in the discussion.

If the non KHDSS area is to be included in this analysis some discussion as to why the in-hospital outcomes were so different should be included.

- We are now only including KHDSS residents in the inpatient analysis, however we did a sensitivity analysis to check if the risk factors for inpatient mortality would be similar amongst children with diarrhea resident and non-resident in KHDSS (Supplementary table 3)

The fact that this analysis developed a predictive model is important and should be reflected in the discussion. Validation is needed if this is to be used clinically.

- Developing a predictive model was not our primary intention inpatient mortality. However, we appreciate that assessing generalizability is important and have added a comment about the need for external validation with datasets from elsewhere in the discussion.
Also a practical method of risk stratification would be needed. Also, some discussion around the kinds of work needed to develop an effective intervention should be discussed.

-We have included an example of current research undertaken by our group to elucidate the mechanisms underlying post-discharge mortality.

Thank you for allowing me to review this interesting manuscript.

Sincerely,

Matthew Wiens, PhD