Peer Review File

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Reviewer A
Comments to the authors:

I applaud the authors for undertaking this important piece of work. There are however some changes which I feel this manuscript would benefit from, for clarity. On the whole, this is well-written. It is a little uneven in tone and content, eg. sometimes the language used is emotive; some statements are opinion and this is not an editorial. This starts off really strongly in the introduction and seems to lose focus a little in different sections. My comments are major & minor as follows:

P=page; L=line.

Major:

1. What type of review is this? From the structure, this appears to a literature or narrative review. This must be stated explicitly somewhere, if not in the title (though that may be an issue of journal style).

Thank you for this comment. We agree that this omission may cause some confusion. We have therefore incorporated this into the title as a narrative review.

2. What literature sources and search strategy were used? Not necessary perhaps if a narrative review, but that has not been stated.

We have now stated in the title, abstract and main body of the paper that this is a narrative review. We have therefore not discussed a literature search strategy. Our research group has competed several systematic reviews on this subject, which are referenced throughout. Our awareness of relevant literature, therefore, is wide on this topic and we feel we have included all relevant references, though we did not conduct a systematic literature search specifically for this review. We did, of course, conduct extensive literature searches while writing this article though there were not systematic in nature, at least as defined by guidelines which outline these types of reviews. We hope that this satisfies both reviewers and the editor.

3. There appears to be a lack of internal consistency as to what is discussed in each section. A senior author should re-read & re-structure this so there is a clearer distinction between sections. For example, the 3rd paragraph of Subsection 2 on Page 12 could as easily be in 'Priorities for future research' rather than in 'Interventional Studies'.

Thank you for this comment. We do agree that in many ways this section, as do several others, do outline important knowledge gaps. Thus, these could also be incorporated into *Section 3: priorities for future research*. We have addressed this by including further comments on long term outcome standardization in this section, while keeping the research gaps outlined in the "intervention" section of the 2nd section the same. The paragraph to which this comment pertains, does, after all, specifically outline a systematic review on post-hospital rehabilitation, which does bear relevance to the section heading.

Minor:

1. I know this has been submitted to a paediatric journal but I think you need to say specify 'paediatric' or 'children' in the title.

We agree that this is an important omission and have included this detail in the title.

2. For the ease of the reader, it might be helpful to be more systematic about how information is presented across sections in relation to neonates or HICs first, then highlighting the gap for paediatric & LMICs.

Thank you for this important suggestion. As we have addressed the reviewers comments, we have done our best to ensure a more systematic approach to presenting our data, including how data on HIV vs LMIC settings is presented. We decided that further systematic sectioning based on HIC vs LMIC was not appropriate since we only occastionally refer to data form HIC, specifically where it further highlights existing LMIC gaps.

3. Throughout, please ensure acronyms are written out in full at their first usage and then used consistently throughout.

Thank you, we have done this now throughout the manuscript.

P4L64: 'Ravages' is very emotive word. "Sequelae" might be more appropriate medical terminology.

We have made this change as suggested.

P5L88: I would defer to journal style here, but the convention for many is that numbers less than ten are written out in full and larger numbers are written as digits. You need to specify units of time here, months or years?

Thank you, this has been corrected.

P6L93: You need to explicitly say 'study design' and the earlier part of the sentence refers to populations.

Thank you, this has been corrected.

P6L95: Is ‘severity’ not what you mean here, not ‘acuity’?

Yes, you are correct. This has been changed.

P6L100-102: This last sentence is not clear. Is malnutrition an independent predictor or a co-variable or both? This sentence does not express that clearly.

We have changed this sentence to read “First, because of it’s strong independent association with mortality after discharge, and second because it is a highly prevalent co-morbidity, thus affecting a substantial number of children living in settings where post-discharge mortality is common.” We hope this add the necessary clarity previously lacking.

P6L106: Sentence meaning is not clear. ‘Diarrhoea + shock in 10%’ and/or pneumonia + shock in 10%’? Were the elevations in inflammatory markers related to the presence of shock?

We agree that this sentence was poorly constructed. We have changed it as follows:

> The link between sepsis and post-discharge mortality was also clearly demonstrated in a recent study of children admitted with severe acute malnutrition, most of whom had an admission diagnosis of either pneumonia or diarrhea.(18) In this nested case-control study from Kenya, a sepsis-like immunopathogenic profile, at the time of discharge, was noted to be common among children who died early during the post discharge period (cases), compared to those who survived without requiring readmission for at least 1 year following discharge (controls).

P6L110: I think saying ‘level of schooling achieved’ is redundant. Most readers would know what level of maternal education means.

We have previously been criticized by for conflating education with schooling, and have thus sought to clarify what we specifically meant by “education”. Education on caring for children could be obtained (and generally is) outside of the context of formal school. We hope the reviewer will allows us to keep this as written.

P6L112: This is emotive language (and not supported by a reference). More neutral medical language might be more appropriate: “challenging”, “incomplete”.

We have changed “arduous and tortuous” to “complex”.

P7L119: How is oncology a co-morbidity of sepsis? It is an aetiological factor surely. That aside, these sentence needs rewriting for clarity.

We agree – this is true. We have rewritten and clarified this paragraph. Issues of co-morbidities as etiologic factors are not very relevant here as we were attempting to highlight the issue among those with no-co-morbidities. We have rewritten this paragraph as follows:

> While post-discharge mortality among children with sepsis is observed most acutely in LMIC settings, issues of persistent vulnerability are observed in both high and low-

income country settings. In the United States, for example, even among children with no known comorbidities, approximately 15% are readmitted within the first 6 months following an episode of severe sepsis, though death is uncommon.(21) Such observations point to both the generalizability of this vulnerability as well the potential preventability of mortality.

P7L133: Same issue with phrasing as P6L106. Even using an Oxford comma would improve this: “pneumonia, diarrhea, or shock in 10% of cases”.

Thank you, we have added this comma.

P7L137: Write ‘6’ as ‘six’.

Corrected.

P8L142: Units? Months or years?

Corrected to years.

P8L143: Write ‘6’ as ‘six’.

Corrected

P8L149: Reduced ‘by 30%’ from what to what for readmission? Is this information available?

Thank you for pointing this out. We have added in the absolute event reduction numbers, and also added in the reference which we had inadvertently not included at the end of this sentence.

P9L175: ‘Impacts on function..’ for long? Was this months or years of follow-up?

This has been corrected. We have changed this sentence to “Indeed, as many as 50% of adults who survive sepsis report persisting negative impacts on cognition and function, as well as psychological deficits and worsening medical conditions, all of which can last months to years following initial recovery”.

P10L1184-186: This sentence seems to contradict the sentence immediately before it. The existence of systematic reviews does not imply recency. Perhaps re-read this paragraph & rephrase (see also comment on consistent sequencing of HIC vs. LMIC and neonatal vs. paediatric studies in all sections).

We have edited this section and re-organized it to sequence it more clearly.

P10L190: ‘Two’ not ‘2’.

corrected

P10L192: “and *a* higher prevalence”

corrected

P10203: this is becoming confusing. You have been discussing quality of life for the various sequelae. What you now perhaps mean are "QoL *scores*" which is a different thing and needs to be stated explicitly.

We have specified that we are referring to scores.

P11L207-211: I do not understand how this paragraph is about long-term data when the quoted study refers to follow-up at 28 days.

We have edited this paragraph to specify that this is the only study we could find and that the measurement period is too short to understand lasting sequelae.

P11L226: NICHD refers to which country? For any acronym, you must write it out in full at first usage within the text.

Corrected

P12L238: This is double-citing, within the text and as a number.

Corrected

P13L265: "operationalize*d*"

Corrected

P13L267: Has 'WHA' been defined prior to this usage?

We have removed this acronym and used the full term (World Health Assembly) for all three instances in the text.

P14L285: This language here reads like editorializing. *How* is it well-positioned.

Thank you for this comment. We have adjusted the sentence to better outline how it is well positioned. It now reads as "Through coordinated efforts to develop standardized terminologies for terms, definitions and operating procedures alongside data curation and analytics, the Pediatric Sepsis CoLaboratory is well positioned word towards more coordinated approach to sepsis research and care."

Reviewer B

Comments to the authors

The authors provide a narrative review of post-sepsis follow up in LMICs, a notoriously understudied subject. They should be congratulated for addressing this. I have a few technical comments and questions.

1) Between Introduction and Section 1, there should be a brief description of how the authors chose their studies. Even narrative (as opposed to systematic) reviews provide some details regarding how the authors chose the articles. Things like databases searched, years included, geographical areas included, an assessment of quality (e.g., "we excluded case reports of < 10 patients" or "we focused on trials and large observational cohorts"). The reader just wants a sense of how you arrived at your conclusions.

Thank you for this comment. We have now incorporated this into our manuscript, as suggested also suggested by Reviewer A.

2) Page 7, line 122 – wasn't the readmission rate after sepsis discharge 47% (not 15%) in this study?

Yes, you are correct, but we are specifically referring to those with no comorbidities, rather than the general population that they were reporting on. This number was visually abstracted from the survival plot (thus we said "approximately 15%").

3) One of the features of LMICs (and even some HICs like the US) is extreme disparity of hospital-level resources. How do the authors envision interventions and collaborations like Pediatric Sepsis CoLaboratory being representative of an entire community, rather than just rapidly adopted by the better-resourced hospitals ina region? Is this even a problem, and is any data better than no data?

This is an excellent point. We do agree that this is a limitation, but also wish to point out that wider attempts at systematically gathering data in LMIC settings, while potentially excluding disadvantaged data sources (either through less funding, weaker infrastructure, or geographical factors), is actually improving the overall diversity of data globally. There is a wide disparity between data generated in HIC and LMIC settings and attempts at narrowing this gap are critically important, even though the gap cannot be wholly eliminated. We have attempted to address this with an additional paragraph in "Section 3: Sub-section 1: Sepsis recognition and data systems". It is the final paragraph of this section.

> An important limitation of any data-dependant initiative is that oftentimes the highest quality data, as well as the highest proportion of data, come from sources that are disproportionately advantaged through funding, human resources, infrastructure or geography. It is therefore important to recognize that the data may not fully represent the population of interest. Efforts should always include an attempt to identify data gaps as well how these gaps may have influenced the conclusions. Despite these limitations, however, the accumulation of high quality and well-defined data remains imperative to advancing sepsis care, especially in LMIC settings, which have often been insufficient for the development of context specific policies and guidelines.

4) More attention should be paid to the pathophysiology of possible immune suppression, potentially compounded by malnutrition, as a driver for death from secondary infections.

A growing body of literature on the complex interactions between malnutrition, immunity and infection is beginning to emerge.(18,19) It is well established that environmental enteric dysfunction, a disorder of chronic intestinal inflammation, is common among children in LMIC settings. Environmental enteric dysfunction leads to a vicious cycle when persistent exposure to poor hygiene environments leads to immune paralysis, recurrent infection and continued intestinal inflammation. Additional work on the intestinal microbiota of malnourished and well-nourished children has suggested an important link between its establishment during gestation and early infancy and outcomes later in childhood.(18,20)

Reviewer C

Comments to the authors:

Dear Authors,

Thank you for your work "Challenges of sepsis survivors in resource limited settings" Overall, this is a unique manuscript in its vision to address post-facility outcomes for sepsis in low and middle income countries. The information to address this topic has clearly been well-investigated. However, as a reader, your manuscript felt disorganized, sometimes redundant, and it was hard to follow at times.

Specifically, I would suggest tying the information you present throughout the paper back to the overall point of your manuscript, as I had to often ask myself how the information presented applies to addressing post-facility outcomes. Throughout the majority of the paper, I was frequently confused and had to re-read sections in order to understand the point being made and its relation to the overarching goal of the manuscript. If you continually come back to the main objective of your paper, you will be able to cut out redundant and only tangientially-related material, shortening your paper, and greatly improving its flow and ease-of-reading.

Thank you for this comment. We have added clarifying content throughout the paper and we hope the reviewer will agree that our changes have made the manuscript less confusing and also better at tying together the "tangential" materials that we think is sufficiently relevant to include.

Additionally, it seems that some information was sometimes extrapolated from citations and certain statements were assumptions, leading me to feel that I needed to verify certain information. I would therefore recommend adding more citations (see below for specifics) or using less definitive language when making personal statements about findings from prior research. In this regard, I would also recommend avoiding making statements such as "robust evidence" without providing multiple citations.

I would not change the title or abstract, it is an excellent outline to the paper.

Lines 31-35: There is no citation that shows the LMIC disproportionate effects of sepsis for lines 30-31 and 33-34. If this is from citation (1), I would recommend updating. Also, the WHO has more updated statistics from 2020 in terms of sepsis, which I would also recommend adding.

Thank you for this comment. We have added in the reference (1) to the first sentence as suggested, in addition to a new reference supporting this claim. In terms of updated statistics, we feel that different data sources (ex. GBD and WHO) have slightly different criteria for how sepsis is defined and how data is captured. We feel that the GBD study, only published about 12 months ago, is sufficiently recent to convey the basic message that (1) sepsis is an important problem, and (2) that LMIC are disproportionately affected. We feel that readers will intuitively accept this as the current situation, despite the fac that the data is from 2017. The trajectory of data, well represented in the GBD analysis further affirms the consistency of this issue, and therefore we feel adding additional details to emphasize this point may not be needed.

Lines 35-36: Seems to contradict the purpose of the paper and what is stated in lines 33-35 and 37-39. What vulnerabilities are exactly pointed out here that are not unique to LMIC but also present in high income countries? Please clarify.

Thank you for this comment. What we are attempting to portray is that the underlying vulnerabilities for morbidity and mortality are also present in HIC, though to a lesser extent. Despite the fact that most of the morbidity is in LMIC settings, this should not mean we ought not to concentrate on similar issues (geography, access to care, etc.) in other settings. We believe that the sentences following this clarify this point, by stating that the burden and outcomes from sepsis are strongly influenced by geopolitical, economic and social undercurrents.

Lines 43-54: The statement that sepsis was a poorly recognized and understood disease process prior to 2017 is not true; Please consider the purpose of discussing “SDGs” without explanation as it requires unfamiliar readers to go to the citation, and read that paper prior to reading this paragraph.

Thank you for this comment. We refer here specifically to public recognition and understanding, not within the medical community (though certainly it could be argued that there has been a growing recognition in this sphere as well).

Lines 55-63: Needs citations. There are a lot of assumptions in this paragraph that have no citations to support it. If there are three aspects being compared, one of which (post- facility

issues) being labeled as “largely neglected in research, practice and policy”, there should be many citations for pre- and facility-focused aspects.

We agree that additional citations would be helpful to justify the statement about the general lack of post-facility (i.e. post discharge) research, practice and policy. We have worked this area for the past decade and are aware of most of the work done in this field. However, its difficult to cite the absence of evidence, but we have cited 1 systematic review which outlines the general lack of post-discharge epidemiology research, especially within the area of sepsis/severe infection. The majority of this review also buttresses this claim by outlining, in the various sections, the general paucity of data on the epidemiology (short term and long term, mortality and morbidity), as well as the lack of interventional work in this area. We believe the reader will, after reading this paper, agree with this claim. In terms of the breadth of work on pre-facility and facility care, it is not the purpose of this paper to outline all this work. The mere fact that sepsis guidelines exist, and that their focus is on facility based care, suggests significant efforts in this area. In terms of pre-facility care, while certainly less robust than facility based care, has been an intense focus of WHO guidelines such as ICCM, as well as other community treatment and referral programs.

Line 69-70: Consider adding more citations for high-income countries when compared to LMICs as 2 citations, both from 2020, do not account for “well-described”, especially considering that citations 10 is a systematic review from 2013 for low- income countries. Lines 77-78 also discuss 13 studies addressing this issue, which is abundantly more than 2 studies for high-income countries.

Thank you for this comment, we have added an additional SLR to the sentence about post-discharge mortality. In terms of additional studies on the long-term outcomes of sepsis, we believe we have provided sufficient citations in this introduction. The subsequent section (Section 2) provides a more robust description of this data.

Line 83-85: Please address why applying sepsis criteria is difficult in LMIC settings because this is then contradicted by lines 87-91, as sepsis needs a source of infection, and thus has many causes.

We are not sure of the contradiction in these sentences. Current sepsis criteria (Goldstein Consensus Criteria) are not easily applied in LMIC settings (they were initially developed for the inclusion of subjects in research studies). Instead of sepsis (regardless of source) being a focus, the focus is on vertical disease-based approaches. Certainly most of those identified through a vertical approach also have sepsis (and this was referenced), this approach neglects the overarching sepsis syndrome and the overarching approach to sepsis care.

Lines 94-102: Are these associations of the authors or reported in literature? Please clarify.

These are reported in the literature, and are the results reported in the systematic review being described. We have added the phrase “In this systematic review, studies demonstrated that…” to this section to add this necessary clarity.

Lines 103-107: The citation does not demonstrate a link between sepsis and post- discharge mortality given the data presented.

We agree this was a confusing paragraph. We have added the necessary clarity to outline our point. The paragraph now reads:

> The link between sepsis and post-discharge mortality was also clearly demonstrated in a recent study of children admitted with severe acute malnutrition, most of whom had an admission diagnosis of either pneumonia or diarrhea.(18) In this nested case-control study from Kenya, a sepsis-like immunopathogenic profile, at the time of discharge, was noted to be common among children who died early during the post discharge period (cases), compared to those who survived without requiring readmission for at least 1 year following discharge (controls).

Lines 116-118: This is out of context in terms of highlighting epidemiology.

Thank you for this comment. We agree that it is not directly epidemiological in nature, but given the prior sentence about the challenges of care seeking and at-home deaths, which are epidemiologic features of an important segment of post-discharge deaths, it seems appropriate to add in this piece of context relevant to leveraging this knowledge for care.

Lines 177-178: In the manuscript, there are more citations for outcomes following sepsis in infants and children rather than PSS in adults, which contradicts this statement. Please include many citations for PSS in adults so they can be directly compared to the later cited studies in children.

We do not believe the number of citations directly reflects the burden of evidence. Since this paper is about pediatric sepsis, it is natural that most citations would be within this context, despite the disproportional degree of research between children and adults.

Lines 180-181: These studies were not done in the NICU, also should not use abbreviations not otherwise described. Furthermore, post-ICU syndrome in children is becoming well-recognized and should be considered as many children in the ICU are there with sepsis. Furthermore, the citations used in lines 184 and 190 do not seem applicable to the overarching goal of this manuscript. Both groups of infants are showing cognitive defects long-term, which by presentation in the manuscript is pointing to the pathophysiology of the hypoxic-ischemic insults from sepsis in neonates.

We have clarified that research on post-ICU syndrome in children in developed countries is growing. There was an error in the citation numbering which has been corrected. We have spelled out NICU in full.

Lines 260-263: I would consider moving this to the introduction.

We have included this definition of sepsis in the introduction (first sentence). This section is focused on terminology, and we believe it's important to emphasize the consensus and controversy around definitions and criteria for sepsis.

Lines 260-272: I needed to re-read this paragraph multiple times in order to understand.

We have made some minor grammatical adjustments here and hope that this adds further clarity.

Lines 316-319: these studies should be clarified whether high income or low-income as many micronutrient deficiencies have been explored thoroughly in RCTs (e.g. ascorbic acid).

Thank you for this comment. We have added clarity that this is for LMIC settings specifically and also this is specifically focused on post-discharge, rather than in-hospital outcomes.

Lines 330-332: This is an assumption that I would be hesitant to make. There are many barriers to getting care, not just health seeking.

We agree that there are many barriers to care beyond health seeking. We have revised this sentence to broadly include access to care as well and also to suggest more work on understanding barriers to care following discharge is required.

> The fact that most post-discharge deaths do not occur in a facility suggest that appropriate health seeking and access to care, at both the individual and health system levels, are important barriers during the post-discharge period. Therefore, efforts to improve the transition from hospital to home, and to also better understand and reduce barriers to subsequent care, are urgently required.

The priorities and interventions outlined in section 3 are very informative, but feel out of context of the paper. I would recommend keeping these, but frequently addressing how these innovations would help improve post-sepsis outcomes *specifically* in LMIC (as many of these interventions can be useful in high income countries as well).

Thank you for this comment. We feel that this section is important to outline the next steps in post-discharge research. We have made several revisions based on the comments of other reviewers and hope that this adds sufficient additional clarity and context.

Reviewer D

Comments to the authors:

Overall, a very well written manuscript. The manuscript is well structured, and it is read well with a nice flow.

The following are my comments

1. The title of the manuscript needs a tweak. The content of the manuscript is more of

discussing about the challenges of managing sepsis survivors (from theperspective of healthcare providers per), rather than challenges of the sepsis survivors. I would also suggest to add “in children” in the title.

We agree and have tweak the title. It is now “Challenges in pediatric post-sepsis care in resource limited settings: A narrative review”

2. The abstract can be made clearer by including more details about the result of the review.

We have limited space in this section and thus are not able to fully address this comment. However, we have attempted to add some additional clarity in this section by adding 2 additional sentences about current gaps in research. Specifically, we have added:

> The paucity of interventional research to improve post-discharge mortality is a clear gap in addressing its burden. A focus on the development of improved data systems for collecting routine data, standardized definitions and terminology and a health-systems approach in research need to be prioritized.

3. The review can be made stronger by adding some details of the methodology and the search strategy.

Thank you. We have added some relevant details about the methodology of the search.

4. Line 176-193: “..research reporting long-term health and quality of life outcomes following sepsis in infants and children is sparce; research on outcomes in LMIC settings, where pediatric sepsis prevalence is the highest, is almost non-existent..” & “..to the best of our knowledge, only two studies have reported specifically on neurodevelopmental outcomes in infants who suffered from sepsis in the neonatal period in LMICs..” These two paragraphs are not quite clear.

We have edited the first of these sentences to make it more clear and then relevant to the second.

5. Line 291- 306: No word of research is mentioned to the proposed intervention in this paragraph though this is under the heading of priority for future research. This could be made clearer.

Thank you for this comment. This section is attempting to frame the context for the next three sub-sections which were specifically about research. Nevertheless, we agree that we have omitted some important and necessary content. We have now added some additional content to this section to address this gap. The last section of this paragraph has now been changed to

> Given these challenges, it is of utmost importance that research initiatives, regardless of the design or the type of intervention, establish appropriate stakeholder partnerships early. A diverse research team, inclusive of representatives from the community, potential implementing partners, local ministries of health, and other relevant organizations or individuals, is essential to the design of research programs with potential for eventual scaling. Later phases of implementation must ensure that health systems within which they are implemented capture key metrics to facilitate both the integration and monitoring of new interventional approaches for post-discharge care.