Author's response to reviews

Title: Integrating sepsis management recommendations into clinical care guidelines for district hospitals in resource-limited settings: the necessity to augment new guidelines with future research

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Dear Dr. Alam,

We are grateful for the reviews of our recently submitted manuscript entitled, “Integrating sepsis management recommendations into clinical care guidelines for district hospitals in resource-limited settings: the necessity to augment new guidelines with future research” (MS#: 1089232450894153). The helpful feedback provided by Professors Myburgh and Maitland has helped to strengthen and clarify the message of our manuscript. The following text is a point-by-point response to their comments:

Professor Myburgh

Minor concerns:

1) In response to the comment regarding limitations of physiologically based recommendations in the absence of high-quality data, we included the sentence “Importantly, the results of studies re-evaluating the efficacy of certain sepsis bundle components (e.g., activated protein C, tight glucose control and low-dose steroids) has led to revision and sometimes removal of these components in more recent iterations of the guidelines” (page 5, line 11).

2) In response to the recommendation to identify potential areas of uncertainty within the algorithm, we added a sentence emphasizing the importance of conducting research to evaluate areas of uncertainty in the guidelines, citing the level of fluid volume resuscitation as an example of such areas of uncertainty (page 8, line 2).

3) Prof Myburgh comments on the inclusion of the 4 figures. We feel that it would be difficult to only discuss the approach in abstract terms without showing the algorithm, particularly to a clinical audience.

4) As suggested, we have highlighted that these guidelines were developed by consensus and recommendations were not necessarily restricted by the lack of a high quality evidence base (page 6, line 37).
Professor Maitland

**Discretionary Revisions:**

1) We appreciate that Professor Maitland agrees with us on stressing the importance of clinical reasoning in the text. We emphasize that clinical reasoning and development of different diagnoses can help avoid inappropriate implementation of the sepsis guidelines on page 7, line 24.

**For consideration:**

2) We agree that future research directions should include evaluating the cost of sepsis guideline implementation to assist front line health workers and administrators in determining how to prioritize resources required for sepsis management. We clarify the point about conducting cost-benefit analyses on page 8, line 29.

3) We agree that previous studies of sepsis are limited in their scope and warrant future multi-site trials to evaluate the efficacy and effectiveness of these guidelines. The revision made beginning on page 5, line 11 addresses this issue.

4) We agree that training health staff prior to implementation of new guidelines is important to ensure that guidelines will make a positive impact on patient outcomes. As suggested, we use evidence from the FEAST trial to support this claim on page 6, line 25.

**Major compulsory revision:**

5) Prof. Matiland makes a compelling point about the generalisability of the FEAST trial. We have therefore modified the discussion to read:

An excellent example of the risk of extrapolating principles of sepsis care across settings was demonstrated by the recent FEAST trial [39]. This large trial involving more than 3,000 African children with severe acute infections showed that children receiving fluid boluses had a higher mortality than children receiving no fluid bolus. This unexpected finding, which arguably may be more generalizable to adults in the same setting than findings from studies performed in developed countries, suggests that validation studies are required to establish the benefit of the IMAI approach which is largely based on lower level evidence. Furthermore, mortality among all patients enrolled in the FEAST trial was strikingly lower (9.4%) than in severely ill children enrolled in previous studies from similar settings (28.2%). This effect may be attributable to targeted training of all health staff on triage and monitoring prior to commencement of the study, and supports the importance of emergency care training of health workers.
We hope that you will agree that manuscript is much improved as a result of these revisions. Thank you again for your consideration.

Sincerely,

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