Author’s response to reviews

Title: Adverse drug events in hospitalized children at Ethiopian University Hospital: A prospective observational study

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Version: 4 Date: 30 April 2015

Author’s response to reviews:

We would like to thank the reviewers for your valuable comments and suggestions. The reviewers have looked the manuscript extensively and much of the concerns are the ones we shared too; might be poorly written or need more details. At the same time very few comments are not addressed in case of disagreements or the message is not clear. The whole document is modified to our best and we would like to hear more, if any, comments. Be aware that the modified manuscript is different from the previous in terms of pages, lines, tables, figure and responses presented in the attached document are based on the original one.

As this is the first study of its kind in Ethiopia, it would have great implications in patient safety considerations; whereas much of our health system doesn’t give an attention in this matter. Thus, this study would be a background for further medication safety programs. It is therefore, an important input for the great body of literature. we are looking forward hearing from you. Point by point responses to comments are outlined as below:

Reviewer 1: Balthasar L., MD, MBA, MPH

Responses are outlined as the order of comments

1. Accepted

2. Corrected in the order of comments as follows

P 5, lines 119: We defined specifically what ADE consisted of and what is meant preventable

• ADE in this study was defined similarly as Bates et al [3]; any incident resulting in injury from a medication. An incident can occur at any stage of the medication
use process (ordering, transcribing, dispensing, administrating and monitoring). A preventable ADE is an injury due to an error at any stage in the medication use - for example, hypoglycemia due to an overdose of insulin. However, non-preventable ADEs weren’t results of an error in the medication process - for example, an allergic reaction in a patient not previously known to be allergic to the medication.

P 5, lines 134/135: we take out that sentence with the sense that it didn’t affect our results; we were pretesting the order of reviewing documents, ADE case evaluation, etc (just for making the collection procedure easy for the data collectors)

P 9, lines 235/236: we have incorporated definitions for severity categories E, F, G, H and I and referenced to include your concern

• The definition utilized for severity categories of ADEs was based on NCCMERP classifications. Severity category E, F, G, H and I refers to temporary harm to the patient requiring intervention, temporary harm to the patient requiring initial or prolonged hospitalization, permanent harm to the patient, intervention required to sustain life, e.g. cardiovascular/respiratory support and death respectively.

-P 9, lines 258: More explanation regarding the logistic regression analysis is added

• To determine predictors for occurrence of ADEs among cohorts, first a bivariate logistic regression between independent variables and occurrence of ADEs was done. The following variables, number of medications ordered, length of hospital stay, age, medication class, presence of infectious disease were considered in the initial analysis. Those variables which showed associations in the bivariate analysis were included in the multivariate logistic regression analysis. Here, the independent effect of each variable on the occurrence of ADEs was confirmed only after adjustment of the possible confounders. Finally, only those independent variables that were persistently associated with the outcome variable were used to construct the final model. Odds ratio (crude and adjusted) with its p-value and 95% confidence interval was reported in the logistic regression analysis. A p-value <0.05 was considered statistically significant.

P10, lines 265...we think now the analysis is clearly described in the methods section and the reader could easily understand the variables considered

3. Corrected as follows

P8, line 208: ‘…about’- deleted

P8, lines 212/213.....this data is picked from the patient’s medical record and that is the clinical judgment by the treating physician. To make it clear, thus we added a phrase ‘......from the patient medical record' in page 6 line 123

P8, line 229/230...we accept reviewer’s comment that the issues he raised
sounds well…the problem arises from not explicitly state the errors occurred during the medication use process that leads to preventable ADE. The other thing here is we missed unintentionally the term 'permanent' for the sentence that the reviewer is so much concerned. ‘…among (permanent) preventable ADEs, three out of four were due to inadvertent route of administration…’. We generally rewritten and incorporated in the modified manuscript. As per your suggestion, we have included a recommendation that emanates from the findings.

4. Figure 1…we appreciate your concern of the way it was displayed. Although we tried to describe the patient recruitment process through figure, at this stage, we feel that we can elaborate it in the results section. And because of that we deleted that table…

Figure 2….corrected
Figure 3…..removed
Figure 4…….changed into table as your suggestion
Figure 5…… As suggested, changed into table

Table 1……..removed, all data are presented in the result
Table 2….corrected

5. We tried to elaborate the method section based on suggestions from reviewers

6. Corrected and now make more clearer

- Regarding predictors of ADEs, we removed the term ‘independent’

7. Limitation now well elaborated

8. P6, line 152… we adapted the trigger tools from US organizations and modified it based on the medicines available in our Hospital, JUSH (Ethiopia). The reference is checked and corrected….

9. Ok

10. P 3 line 71 and others with some figures, comment accepted and consistent use of digits was done throughout the manuscript

P4, line 114 and P5 line 127, the abbreviation ‘hrs.’ was written out

P5, line 127 corrected

P5, lines 138 and 139 corrected

P5, lines 141/142 corrected

P7, line3 191 corrected

P5, line 203 corrected
P 10, lines 273/274…rewritten and modified as…

• ……. Besides, the lack of gold standard method for ADE detection limited comparison across studies. And the scarcity of literature in developing countries restricted us to evaluate our ADE occurrence in similar settings with low socioeconomic status…..

P11, lines 305-307 corrected and modified to some extent

P11, lines 307-308 deleted

P11, line 309 modified as your suggestion

Reviewer 2: Mio Sakuma

Major compulsory revisions

1. Ok, rewritten

2. Corrected and definitions incorporated for ADEs, preventable ADEs and severity

3. The data collection tool was developed by the authors of this study. For your information, four data collection formats were used in this research project. Authors developed data abstraction checklist for socio-demographic, diagnosis and medication therapy. The data collection tool for ADEs was a modification of the national ADE reporting format. Additional formats include pediatric ADE patient record review sheet, ADE monthly summary sheet form, medication error reporting /data collection form as well as open and close ended interviewer administered questionnaire translated to two commonly used local languages which is used to solicit information from children /parent or relative regarding previous reports of ADEs and medication history as well food related allergies. However, to make the methods section brief and concise, we have rewritten it as…” For the purpose of this study, a data collection tool was developed.”

4. Yes, 1 nurse and 2 pharmacists were involved in detecting ADEs. We think that this is explicitly described in the methods section. ADE was detected in a multifaceted approach

- Daily chart review and interviewing mother/patient attendants: 1 nurse and 2 pharmacists were responsible

- Attendance at multidisciplinary ward rounds/ meetings: the principal investigator was responsible

- Voluntary and verbally solicited and unsolicited reports from pediatric ward staff

All of the above multi-method strategies for identification of ADE are described

5. We appreciate the concerns but we strongly disagree reviewer’s comment
regarding involvement of PI. PI of the study only attends rounds and clinical meetings to solicit any alerts for ADE and does not involve in decision making for the day to day clinical care. He is not involved in any clinical pharmacy activities. We believe that communication of pediatric team about the study for voluntary report of ADE occurred in the ward will not have any bias rather it will increase yield as voluntary report of ADRs is one of the well-established method of ADR reporting. The other thing is we contacted physicians whenever there is any medication dose change because we believe such interventions might be related with ADEs as a trigger tool. Documentation of physician’s interventions for management of already identified ADE, we believe, does not introduce any bias on the incidence and severity. It is also our ethical principle that patients who faced any ADE should receive appropriate management even if such intervention has any impact on the severity of identified ADEs.

6. Accepted, elaboration on the logistic regression analysis was included in the revised manuscript

   • Cutoff points for variables were considering clinical significance of the cut off values and based on other literature reports.

7. We have included different measures of incidence rates as it will help us to compare with other similar literature findings. There is lack of homogeneity among previous studies on the denominator to calculate the incidence rate for ADEs. Some of the studies use per 100 admissions, some per 100 patients, per 1000 patient-days, per 1000 medication doses. For this reason, we tried to use as much as possible literature reported denominators. That is why; the reviewers pointed that why we used both admissions and patients. Since it was a 3 month study, one patient can have more than one hospital admission during the study period. If we only consider incidence of ADEs per 100 patients, incidence rate per 100 admissions might not be same that is why we intended to include the two denominators. Here in our study, we have 600 patients who had 634 hospital admissions, i.e. some patients have repeated hospital admission during the study period. Hence, a total of 634 admissions representing 600 patients were included. Twenty nine patients had > 1 hospitalizations during the study period. i.e., 34 hospital admissions were repeated hospitalizations.

8. Each ADEs were treated in the analysis as a separate independent ADEs.

9. Comment accepted, these events are due to medications the patient was taking while admitted and still the ADEs continues to happen in the ward and hence we included in the analysis.

10. There isn’t a sentence describing phlebitis with swelling and redness as a non-preventable ADE. Probably the sentence ‘…of those ADEs…’ mislead the reviewer and understand that ‘…those ADEs…’ (as non-preventable). But now more modification in sentence arrangement was made and things are clearer than before.

11. Accepted
12. Accepted: comment incorporated, it is described in results section (Table 1 is deleted)

13. Accepted and corrected

14. Accepted and results are reported in the appropriate section

15. Accepted: statement is deleted as it has little significance to the scientific community but it should be clear that figure 4 describes ADEs based on sign and symptoms and not in terms of organ system affected by ADEs.

16. It is not clear….We clearly showed that patients weren’t included if the hospital admission was less than 24 hr. Otherwise, ADE detection approaches were the same for all patients

17. Accepted

18. Comment incorporated and some modification on the manuscript

Minor essential revisions

1. Reference 22

2. Because of less relevance, we deleted that sentence but to mean that nurses are allowed to collect supply of medications for admitted children only 24 hour dose from pediatric pharmacy.

3. Definition included incidents/events are synonym words in this study

4. MDT team includes attending senior physician, residents, nurses and pharmacists. Principal investigator and data collectors will interview either of these team members depending on expertise whether there involves ADEs in the specific patient. Their role in the study was to help explain patient conditions when ADEs are suspected in the patient they follow when additional information is needed.

5. Comment incorporated in methods section: analysis part

6. Corrected: 55.4 medication doses per admission not per patient

7. We preferred mean because most references we used to compare report mean, so for ease of comparison, we preferred mean

8. Number of medication ordered considered

9. There is no any arithmetic error: 9.2 per 100 admissions is correct…not 9.2 per 100 patients

10. Comment accepted and done

11. Table 1 is already removed
12. Corrected

13. Figure 5 is now expressed in terms of table

Discrepancy revisions

1. Comment accepted and examples incorporated

2. Comment accepted and table added for the stages of errors with specific examples