Reviewer's report

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

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Reviewer's report:

Chanie et al present a paper on adverse drug events (ADEs) in a children’s university hospital in Ethiopia (Jimma University Specialized Hospital, JUSH). The topic is timely, although there have been published many studies internationally in this field. However, studies on ADEs from Africa with focus on children are still rare and badly needed.

The study is well done; however, there are some major and minor aspects that have to be reconsidered before publication. This review follows the BMC guideline points for research articles with comments marked **.

1. Is the question posed by the authors well defined?
   **The question is well defined and clear: What is the incidence and nature of ADEs at JUSH?

2. Are the methods appropriate and well described?
   **The methods are only partially described and do have to be completed:
   - P 5, lines 119 and following: The authors should give a clear definition of adverse drug events; it is not sufficient to refer to literature on that giving 6 references. Which one did they follow? Definitions differ quite a bit according to reference. How did they define a « preventable » ADE? All these definitions must be stated clearly for the international reader.
   - P 5, lines 134/135: here the reader learns about a « data collection tool » that was « pre-tested » and « amended ». What did the authors do here? What had to be amended? The authors should explain that in detail for the reader.
   - P 9, lines 235/236: Here the reader is surprised by an ADE severity index with categories E, F, G etc. We find a table in the supplement but without any reference. Although this is an international severity scale it has to be explained in the methods section and properly referenced wherever it appears.
   - P 9, lines 258 and following: Here the reader learns that a univariate logistic regression analysis and a multivariate model analysis were done. Again, these procedures must be described in the methods section, how they were done, which and how many parameters included in the multivariate model. Since we have 58 outcomes the number of parameters will have to be restricted.
   - P 10, line 265: Here we read about a « full model analysis ». Again, this has to be described in the methods section including information about which and how
many parameters and which parameters the authors adjusted for.

3. Are the data sound?

**The data can be followed through in general, but there are some points that definitely need clarification:

- P 8, line 205, minor: « The mean length of hospital stay and medications ordered was about 9.8 days (± 8.8 SD) and. “ Why do the authors write „about“? This number is supposed to be computed by statistics and not to be approximative. The word „about“ should be left away.

- P 8, lines 212/213: « Of 634 admissions, 104 (16.4%) and 75(11.8%) were found to be stunted and wasted with different degree of severity respectively.“ The authors should explain to the international reader what „stunted“ and „wasted“ mean in this context (loss of weight? Vitamin deficiencies? Growth retardation?) and how they defined the two expressions exactly for the study protocol. Or was this a clinical impression by the treating physician?

- P 8, lines 229/230, major: “Among preventable ADEs, approximately 75% of them were due to inadvertent route of administration.” The word „inadvertent“ means „not intended or planned“. The authors are saying that three out of four preventable ADEs were due to wrong administration of drugs? The wording should be more clear at this point. If this should be true, then education of the health personnel should be a main target for prevention of ADEs. This implication should be stated in the conclusions paragraph.

But then, looking at the discussion section, the authors write (p 10, lines 292-294) „In our study, the primary medication error responsible for preventable ADEs was improper dose while the most common medication use process was the administration stage.“ Now, this is confusing and not congruent with what we have been told on p. 8. What is true now „inadvertent route of administration“ or „improper dose“? This is not the same!

4. Do the figures appear to be genuine, i.e. without evidence of manipulation?

**There are five figures and three tables displayed.

- Figure 1: Patient flow chart: This is an important asset in a study, but the numbers here are not congruent and confusing the reader: of 699 admissions 634 were followed because of the exclusion of 65 with insufficient data or a length of stay <24 hours. The next box is confusing, since here the authors start talking about patients and admissions; they should stick to admissions. But I cannot follow the math: 634 admissions minus 63 admissions in 29 patients would result in 571 admissions, but the authors mention 634 admissions. Or do they just want to mention that 29 patients account for 63 admissions and that’s it? If yes, they should provide this information in a footnote. But why do they draw an arrow to the right? Internationally, this is understood as patients being withdrawn for some reason. Thus, this flowchart has to be clarified and stated clearly where admissions had to be excluded and what is additional information.

- Figure 2: This is a fine and important figure. Absolute numbers should be added to the percentages and the footnote below the « Infant » column is
- Figure 3: These photographs should be called photographs and not «Diagrams» in the title. I think they are interesting to see but could as well be left away, since most physicians and nurses know how a phlebitis and extravasations look like.

- Figure 4: This figure does not add additional information and should be presented as a small table with a line describing all ADEs with N=1 together (the majority of them).

- Figure 5: This figure should also be presented as a small table since it is supposed to contain important information. However, the most basic informations are missing in this figure: the absolute numbers, the percentages on the columns and which drug classes.

- Table 1: This should be merged with table 3 and offered together as table 1 with the basic information about the children’s cohort. In table 3 the reader should know what the OR was «adjusted» for (age? LOS? etc). Furthermore, the international reader should know how the diseases in table 3 are coded; is a DRG system or an ICD coding system in place? Or are these just clinical diagnoses («presence of infectious disease»)? There are several typos in table 3 like «NO» at «CNS medicines», «Use of anti-histamine and ant-allergic» drugs instead of anti-allergic.

- In table 3 I am not positively convinced that the OR of 21.9 unadjusted and 32.5 for use of anti-histamines and anti-allergic drugs in the adjusted analysis are correct. I suppose it is because the N=10 (=0.5%) prescriptions (see table 2) is extremely small. We can recognize this statistical problem also in the huge confidence intervals of 5.9-80.7 unadjusted and 5.9-176 in the adjusted analysis. The authors should reconsider this part of the analysis or if they want to collapse these drugs with other classes.

- Table 2: is fine except that the reader should know what substance «calvitalis» is and whether in Ethiopia the same ATC codes are used as in Europe or different ones?

5. Does the manuscript adhere to the relevant standards for reporting and data deposition?

**The reporting of data seems adherent to international standards. The data base is just partially described in the methods section; the authors should expand on that as described regarding the methods section.

6. Are the discussion and conclusions well balanced and adequately supported by the data?

**Generally they are balanced. However, there are some points that are unclear and need to be adapted in the manuscript:

- One of the main findings seems to be that three out of four preventable ADEs were caused by wrong application of a drug (see above point 3). This should be stated clearly in the conclusions section with the consequence of better education of nurses/doctors in this regard. Later, in the discussion section on p.
10 this result is replaced by saying that reversible ADEs were primarily caused by « improper dose ». This contradiction is confusing and robs the paper of credibility. Furthermore, why are these main results nowhere to be found in tables?

- Towards the end of the discussion (p. 12, lines 341-43) the reader learns that « .. our finding shows the association of use of CNS and endocrine medicines as well as presence of infectious disease as an independent correlate for ADE occurrence."

I do not agree with this conclusion, because where antiinfectives are the most common drugs used we will find ADEs with mainly these drugs. Similar findings were present in community hospitals in the US where cardiovascular drugs were preeminent(1). Therefore, there should be a sentence added with this precaution or the word „independent“ left away.

- 7. Are limitations of the work clearly stated?

**There is a limitations section on p. 12. This section should be expanded with the following aspects:
- that it was a single center study and therefore might not mirror results from other hospitals;
- single country study that might not be generalizable to other countries;
- ADE drugs detected mirror the drugs used, see comment above.

8. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished?

**Generally, the paper is well referenced. There are some modifications needed, though:
- P 6, line 152 : an « Annex » is mentioned regarding medicines available in Ethiopia, but there is no information about this in the paper. The authors should make this information available to the reviewers and the readers either in the manuscript or with an online link.
- In the supplement we find trigger information. This information should be referenced; some of it stems from the IHI Trigger tool from the US. The same is valid for the ADE severity scale in the supplement; references should be added.

9. Do the title and abstract accurately convey what has been found?

**The title is correct and conveys the contents of the study.

10. Is the writing acceptable?

**The writing is generally fine, but there are many corrections needed and the manuscript should be read and corrected by an native english speaking person:
- P 3, line 71 : the authors should be consistent and use one digit after the percentage points throughout the manuscript and not two.
- P 4., line 114 : « hrs » should be written out in the text; also on p 5, line 127.
- P5, line 127 : « Except in weekends… » should read « Except on weekends…
», also on lines 138 and 139.

- P 5, lines 141/142: « data on drug exposure.. » rather than « data about drug exposure ».

- P7, line 191: « During the data collection process; patient intials were... » The semicolon should be cut out since it does not make any sense.

- P 5, line 203: « A total of 35,117 medication doses were given to the above patients; accounts for 55.4 medication doses per patient." Instead of the semicolon and „accounts“ it should read „accounting for...“.

- P 10, lines 273/274: « The absence of gold standard methodology to evaluate incidence of ADEs; however, restricted comparison of our findings to those studies that used very similar methodology.“ There are two verbs missing in this sentence.

- P 11, lines 305-307: « Thus, the severity of ADEs, in our study, is much serious than those in the literature and of which, 9% were resulted in permanent harm/death." This is an odd sounding sentence; better would be something like „Thus, the severity of ADEs is much more serious in our study than those in the literature..” and „...9% resulted in...“ instead of „were resulted“.

- P 11, lines 307-308: « So, the impact of ADEs on children in our hospital would be significant than other similar studies.“ I would leave this sentence away; it does not add any new information.

- P 11, line 309: «...severity of the harm was higher than previous reports." should read something like „higher than in previous reports“ or „higher than most previous reports".


Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare that I have no competing interests.