Author’s response to reviews

Title: Risk factors for recurrent severe anemia among previously transfused children in Uganda: an age-matched case-control study

Authors:
Aggrey Dhabangi (adhabangi@gmail.com)
Richard Idro (ridro1@gmail.com)
Chandy John (chjohn@iu.edu)
Walter Dzik (SDZIK@mgh.harvard.edu)
Robert Opoka (opokabob@yahoo.com)
Ronald Ssenyonga (rssenyonga@musph.ac.ug)
Michael van Hensbroek (mbvh04@gmail.com)

Version: 1 Date: 04 Jan 2019

Author’s response to reviews:

Manuscript ID: BPED-D-18-00982

Title: Risk factors for recurrent severe anemia among previously transfused children in Uganda: an age-matched case-control study

Corresponding author: Aggrey Dhabangi

Response to reviewers’ comments

Reviewer: # 1

Thank you very much for your insights in the African Pediatrics. My few comments are the following:

1. Line 137 please eliminate;

Authors: Corrected. Thank you

2. Line 138 please put, after urine
Authors: Corrected. Thank you

3. Line 141 FBC (Full Blood Cells): put this acronym in the list of abbreviations
Authors: We have fixed this. Thank you

4. Line 172 Table instead of table
Authors: Corrected. Thank you

5. Line 172 about ACTS, do you mean ACTS use prior to admission?
Authors: Yes. We have fixed this, including line 202.

6. Line 184 about nine variables, clarify better this point
Authors: The variables with a p-value <0.2 were ten. We have corrected this, and in response to the reviewer’s suggestion, we have added text – in brackets, enumerating the ten variables, as follows: “All variables with a p-value <0.2 at bivariable analysis (hemoglobinuria, sickle cell anemia, history of earlier previous blood transfusions [in the period >6 months], malaria diagnosis at current admission, passage of dark or red-colored urine, mother’s age, ACTs use prior to admission, malarial anemia at most recent admission, history of other previous admissions, and suspected bacteremia) were entered into a stepwise backward conditional logistic regression model.”

7. Line 186 Table instead table
Authors: Corrected. Thank you

8. Line 221 please eliminate;
Authors: Corrected. Thank you

9. Line 229 please eliminate;
Authors: Corrected this too. Thank you

10. Line 249 please eliminate;
Authors: Corrected. Thank you

11. Line 259, please clarify better comprehensive investigations

Authors: We meant further investigation. We have changed text accordingly.

12. Line 261 Abbreviations please put in alphabetical order and insert FBC

Authors: Thank you. We took the change as suggested.

13. Line 335 about variable sex, I think you inverted cases with controls. The number of cases is 95 instead of 101, the number of controls is 95 instead of 101. Please check them. Authors: We have cross-checked, and found that the reviewer was right on this one. We have corrected it accordingly.

14. Line 338 idem as mentioned above. Please check these data! In the table 2, about the variables No of meals per day and mother's age, the number of cases and controls are lower. Are this information lost? I think you might comment about this point.

Authors: We have cross-checked the data. For some variables, such as No. of meals, mother’s age, and others; the reason why the totals in each category of cases and controls do not make up to 101 and 95 respectively; is because of responses coded as N/A (not applicable) or DK (don't know) in the case report form. For example, where the caregiver was not the mother, sometimes they did not know these details, e.g age of the mother, or when the mother was deceased, etc.

15. About History of earlier previous transfusions, the sum of controls is 96 instead of 95. Please check the data!

Authors: This was a typo; 79 rather than 78 - for the controls with no history of previous transfusion. We have corrected to 78.

16. In general, you might comment more deeply the discussion, the limitations and the need of further research in this field.

Authors: This is a good comment. To follow this suggestion, we have now added text to the limitation and recommendation/conclusion sections, as follows: “Similarly, the fewer numbers tested for variables such as reticulocyte production index further limits the power”…. and “Generally, the problem of recurrent severe anemia among children merits further investigation, including areas such as the cause of hemoglobinuria and its potential relationship with prior ACTs use” respectively.
Reviewer: # 2

A. Just to verify: did the controls have previous blood transfusion also??

Authors: Yes. See line 31-32 of the abstract: “We prospectively enrolled 196 hospitalised children who had been transfused for severe anemia 2 weeks to 6 months prior to enrollment”. A similar phrase is found at line 93-95 of the methods section.

B. Table 1: The highest number of both cases and controls were from Jinja, is this the largest city with the major population??

Authors: Jinja hospital serves as a regional referral hospital in east-central part of Uganda. In terms of malaria epidemiology (since malaria is a major cause of severe anemia and recurrent severe anemia among children), Jinja is a high transmission area (Kamya MR, Arinaitwe E, Wanzira H, et al 2015, and Okello PE, van Bortel W, Byaruhanga AM, et al 2006)

C. Table 2:

* History:

C1. More controls have history of malarial anemia at most recent admission compared to cases?? Why was that? Cases are expected to have that history.

Authors: Indeed this was an interesting finding. That is why this factor seems protective [Crude odds ratio of 0.39 (0.15-0.98)]. But as we mentioned in the discussion (at the end of the 1st paragraph) Phiri KS et al 2008 has also found a similar thing.

C2. History of earlier previous transfusions: 51.5% of the cases and 82.1% of the controls have no history of previous transfusion. I understood that all cases and controls had history of previous transfusion (2 weeks-6 months prior to enrollment).

Authors: Good comment. The variable ‘earlier previous blood transfusions’ refers to blood transfusions in the period >6 months, since both cases and controls alike had had been transfused within 2 weeks to 6 months prior to enrollment. To clarify this point, we have re-phrased the text (line 171) as: “History of earlier previous blood transfusions (in the period >6 months)...”. The same text ‘(in the period >6 months)’ has been added at line 185, 190, and 205.

C3. * At current admission:

- Suspected bacteremia between cases and controls was non-significant (P= 0.06).
Authors: Correct. We have now deleted this variable from the list of factors independently associated with RSA, at line 175 and 207.

D. Discussion:

D1. It is written on line 174-175: suspected bacteremia was independently associated with RSA but no statistical significance was shown in the table.

Authors: Thank you for raising this. We have fixed this in response to C3 above.

D2. Line 206-207: it is written that "75% of cases had a diagnosis of malarial anemia at the most recent prior admission". Also, 81% of controls have that history. How can this item in history make a difference between cases and controls?

Authors: We have responded to a related comment (C1) above.

E. Is G6PD deficiency common in Uganda?? It is good to test those cases for G6PD too to know if this was a contributing factor.

Authors: In some parts of Uganda, the prevalence of the gene has been estimated to be about 7.7% (homozygous) [Bwayo D, Kaddumukasa M, Ddungu H, Kironde F, 2014]. In our study, we were limited by funds to test for G6PD deficiency. However, because G6PD deficiency is an X-linked gene, we attempted to check for interaction between hemoglobinuria and sex; which we found to be not statistically significant (see last paragraph of the results section).