Author's response to reviews

Title: Human immunodeficiency virus infection is a risk factor for cerebral malaria in children in Uganda: a case-control study

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Author's response to reviews: see over
Dear Editor,

I would like to thank the reviewers for their great comments and concerns. I have attached herewith a copy of my revised manuscript for a study titled “Human immunodeficiency virus infection and cerebral malaria in children in Uganda: a case-control study” for publication in BioMed Central Pediatrics for re-evaluation for publication after addressing the reviewers comments.

With the submission of this manuscript, I would like to undertake that the above mentioned manuscript has not been published elsewhere, accepted for publication elsewhere or under editorial review for publication elsewhere; and that my Institute’s (Makerere College of Health Sciences) representative is fully aware of this submission.

This submitted manuscript is a research article.

The research project was conducted under the supervision of:

1. Prof. James K Tumwine, professor of Paediatrics and Child Health, Department of Paediatrics and Child Health, Makerere University College of Health Sciences, Kampala Uganda, kabaleimc@gmail.com

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The research project was part of my Master of Medicine (M.Med) in Paediatrics and Child Health thesis and was conducted from November 2006 to March 2007.

My Research Project was partially funded by the Malaria Consortium, Uganda and personal funds. This work has not been published before but was presented at the 13th International Congress on Infectious Disease in Malaysia June 2008 (poster presentation) and at the International AIDS Conference in Mexico, August 2008 (oral and poster presentation).
The significant findings in this article were that the prevalence of HIV infection in cerebral malaria was 9% and the risk of developing cerebral malaria in the HIV positive children was 4.98 (95% CI 1.54-16.07; p-value =0.003.

This was the first study done in children to determine whether HIV infection is a risk for developing cerebral malaria. Other studies had been looking at severe malaria in general and were mainly conducted in the adult population.

Changes made to the manuscript following reviewers’ comments:

**General**
- Replaced “associated with the development of cerebral malaria” a with associated with “clinical presentation of cerebral malaria”
- Corrected grammatical mistakes

**Abstract**
Revised to incorporate adjusted odds ratios, and also results and conclusions revised

**Background:** Human immunodeficiency virus (HIV)-1 infection increases the burden of malaria by increasing susceptibility to infection and decreasing the response to malarial treatment. HIV-1 has also been found to suppress the immune system and predispose to severe forms of malaria in adults. There is still a paucity of data on the association between HIV-1 infection and cerebral malaria in children. The aim of this study was to determine whether HIV-1 infection is a risk factor for cerebral malaria in children.

**Method:** We conducted an unmatched case-control study, in which 100 children with cerebral malaria were compared with 132 with uncomplicated malaria and 120 with no malaria. In stratified analyses we estimated odds ratios (ORs) and 95% confidence intervals (CIs) adjusted for age.

**Results:** HIV-1 infection was present in 9% of children with cerebral malaria compared to 2.3% in uncomplicated malaria (age-adjusted odds ratio (aOR) 5.94 (95% confidence interval (CI) 1.23-28.72, p=0.012); and 2.5% in children with no malaria (aOR 3.85 (95% CI0.98-15.07, p= 0.037). The age-adjusted odds of being HIV-positive among children with cerebral malaria compared to the control groups (children with uncomplicated malaria and no malaria) was 4.98 (95% CI 1.54-16.07). The association was seen among HIV-positive children with a relatively normal or mild immune suppression compared to those with moderate to severe suppression. Other factors associated with cerebral malaria were age and parasite density.
**Conclusions:** HIV-1 infection is associated with clinical cerebral malaria in children. Cotrimoxazole prophylaxis in HIV infected should be emphasized since it also has protective effect against severe forms of malaria. More studies should be conducted to determine the correlation between cerebral malaria and level of HIV-1 immune suppression.

**Background**

**First paragraph**

Added references for overlap between HIV and malaria in SSA and for studied in malaria and HIV done in adults:

Malaria and Human immunodeficiency virus (HIV)-1 are two of the most common global health challenges today and the two infections commonly overlap in distribution in most countries especially in sub-Saharan Africa (1). Studies have demonstrated interaction between these two infections with the majority of studies conducted in adults (2-5).

**Paragraph three**

References added to first sentence: Malaria-specific antibodies which the main target of protective malaria immunity seem to be little impaired in HIV infected but in advanced AIDS, evidence indicates B-cell stimulation is diminished to some extent, resulting in decreased production of malaria antibodies (9-11).

**Methods**

**Paragraph 1: Clarified statement in paragraph one:** Severe anemia was not an inclusion criterion per se but children with severe anemia, who had history of convulsions and were admitted with a BCS ≤2 (in coma), with a relatively normal blood sugar (at least above 2.2mmol/l), normal electrolytes and a normal CSF with a positive blood smear for malaria parasites were taken as having cerebral malaria.

**Paragraph 3:**

A trained counselor was available to do both pre- and post-test counselling for HIV. Five millilitres of blood were drawn from each child with cerebral malaria and uncomplicated malaria for a malaria smear, *P. falciparum* parasite density, HIV serology and CD4 cell count, blood glucose and serum electrolytes. A finger prick was done for children with no malaria for the blood smear and rapid HIV test and 2-3 millilitres for CD4 count if the child was found to be HIV positive.

**Tables and figures:** Tables were revised, and all baseline characteristics fitted into one table (table 1). Parasite density was adjusted for age and both unadjusted and adjusted OR represented in the table. White cell count is not available for the patients.


The entire results, discussion and conclusions and recommendations sections were revised as recommended by the reviewers.

**Results:** Adjusted the odds ratios for age (a potential confounding factor), also including the analysis including only children below the age of five years.

Among children below the age of 5 years, the HIV prevalence in cerebral malaria cases was 8.6% (7 of 81) compared to 1.2% (2 out of 166) among all controls. The odds of presenting with clinical cerebral malaria below the age of five was higher among children who were HIV positive compared to the HIV negative counter parts OR=7.76 (95% CI; 1.52-39.47); p-value 0.003 (Table 3).
Conclusions and recommendations
HIV-1 infection is associated with clinical presentation of cerebral malaria in children. HIV positive children should be initiated on cotrimoxazole prophylaxis as soon as they are diagnosed with HIV and should be counselled on adherence. In addition, use of mosquito nets in children especially below the age of five should be emphasized during counselling sessions.

Also added to the manuscript are:

Potential conflicts of interest: The authors declare that they have no competing interests.

Authors' contributions: PDI conceived and designed the study, performed analysis and interpretation of data and drafted the manuscript, PM, JB and JKT assisted with the design, interpretation of data and the critical review of the manuscript. All authors read and approved the final manuscript and participated in its revision.

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