Author’s response to reviews

Title: Incidence, causes and phenotypes of acute seizures in Kenyan children post the malaria-decline period

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Version: 1 Date: 07 Sep 2015

Author’s response to reviews:

The editor,

BMC Neurology,

7th Sep, 2015.

Dear Dr Tobias Engel,

Re: Incidence, causes and phenotypes of acute seizures in Kenyan children post the malaria-decline period

Thank you for the expeditious review of our manuscript and for the opportunity to address the reviewer’s comments. We have responded point by point for each comment as below. The changes have been updated in the manuscript and are highlighted in yellow colour.

We can confirm that this paper is not published elsewhere and is not being considered by any other journal and that all the authors have read and approved the final version of the paper. We declare no conflict of interest.

We look forward to hearing from you.

Yours sincerely,

Symon M Kariuki on behalf of the authors
Reviewer 1:

Reviewer #1: Serem and colleagues examine data on admission of children with acute seizures to a Kenyan hospital. The background to the study is that malaria rates have declined in recent years and this would be expected to lower rates of admissions of children with acute seizures. The authors report data on the incidence of seizures for > 2000 children over a 5 year period. They provide estimates of prevalence and cover different types of acute seizures and their suspected causes along with other useful information on neonatal seizures and mortality. Their primary conclusion is that rates of admissions increased during the period. Overall, this is a useful dataset. I have the following comments:

1). Please mention why and how malaria causes acute seizures. Is this an indirect effect of infection-related immune or pyrexic responses or direct effects of the pathogen? There are many possible mechanisms by which falciparum malaria causes seizures [1]. It can cause seizures because parasite infected erythrocytes sequester in the brain causing diffuse brain damage that may manifest as acute symptomatic seizures [2]. Falciparum malaria infection down regulates GABA receptors thereby increasing susceptibility to seizures [3] and its associated febrile temperatures and inflammatory molecules may lower the seizure threshold. In addition hyponatraemia and hypoglycaemia, common complications may precipitate seizures. It is likely that all these mechanisms are involved in the pathogenesis of malarial seizures, but the role of fever remains unclear since most seizures occur when the child is afebrile [4]. We have clarified this in paragraph 2 of page 4 of the manuscript.

2). The authors should state what the incidence of acute seizures in children/neonates was before the decline of malaria in the region (e.g. in Introduction). How great a reduction in malaria rates has there been in the region? In Discussion, the authors state their incidence rate (312/100,000) is comparable to that in a previous study (425/100,000) but this is a substantially lower rate. So, have rates really increased? We have mentioned in that the incidence of acute seizures was between 425-650/100,000/year in paragraph 2 of page 4 of the revised manuscript. We have explained that the incidence rate of 425/100,000/year is higher than the 312/100,000/year in our study since the former is from period when malaria transmission was still high (from 2004-2006). Our incidence estimate of 312/100,000/year is from 2009-2013, soon after malaria declined, during which there is some evidence that the burden of hospitalised malarial seizures could be increasing. We have clarified this point in paragraph 1 of page 11 of the revised manuscript.

3). With what degree of certainty are assumptions about what probably caused the seizures made?
Thank you for this important point. These causes should be considered as “proximate causes” since (i) they are already known to cause acute seizures in previous studies in the same area and in the literature and (ii) they were identified by a panel of clinicians/neurologists through a consensus before discharge or soon after a child died. With logistic regression modelling, we estimated that >90% of seizures in a parasitaemic child are caused by the malaria parasite [5].

4). The authors used the 1989 ILAE standard definitions for their classification. In light of the 2014 published definitions/standards, would this change anything substantially?

The definition of acute symptomatic seizures is similar between these documents [6, 7]. We have indicated this in the methods section.

Reviewer #2: This study is to demonstrate the incidence, causes and phenotypes of acute seizures in Kenyan children post the malaria-decline period. The findings include an increase in incidence of seizures attributable to malaria or not, and a high mortality associated with neonatal seizures (10%) and complex seizures (8%). Causes of all acute seizures were malaria (33%) and respiratory tract infections (19%). However, as the authors have mentioned, it's a hospital-based study and hospital accessibility adversely affect its accuracy and reliability. That's why there are some results difficult to interpret in comparison with previous publications. Besides, in figure 2, "incidence per 1,000 live birth" should be changed to "incidence per 100,000 live birth".

We agree with the reviewer that hospital studies are unrepresentative of the situation in the community as they are likely to be biased towards severe morbidity. We have discussed this explanation in the limitation section. Additionally, we have set up studies to understand the burden, causes and outcomes of acute seizures in the community. We have revised the inconsistency in figure 2.

References


