Author's response to reviews

Title: The incidence, aetiology and outcome of acute seizures in children admitted to a rural Kenyan district hospital

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Version: 2 Date: 3 December 2007

Author's response to reviews:

03 December 2007

Dear Editor BMC Pediatrics

Re: Reply to Reviewers comments

Below is a point by point reply to queries raised by the reviewers and the changes that we made to the manuscript. In addition, the tables have also been formatted as suggested.

Review 1

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

Materials and Methods section:

1. How many cases receive CSF study? Is CSF study performed in every case or in only cases with acute symptomatic seizure?

On page 6, we indicated that lumbar puncture was performed according to a published protocol. To clarify this further a summary of the protocol has now been included in the text. A total of 594 children out of the 900 (66%) had LP performed.

2. Lines 1-3, on Page 6, did every case receive the complete studies which you mention in the manuscript? How many amount of blood samples are collected in every case, especially in sick neonate?
Blood samples were collected on almost all patients. Although on average about 5 ml was drawn, the volume taken varied with weight and the ability of the child to tolerate the procedure. This ranged from 2-7ml. Blood culture contributed for most of the volume in all children. Thus very low birth weight infants had at most 2mls taken of which about 1 ml was sent for culture. Our protocol for blood draw has been attached for reference.

3. Lines 10-13, second paragraph in the Methods section on Page 6, therapeutic guideline for malaria and bacterial meningitis in your study should be described in detail, including duration and dosage of antimicrobial agents.

Details of the protocols of antimicrobial therapy used have been provided in the text on page 7.

4. Line 8, first paragraph of the section on Page 7, you mentioned, ¿We then compared the clinical and laboratory features and the diagnoses in patients with and without seizures to describe the clinical risk factors for seizures and examined the risk factors for poor outcome¿. Please define ¿poor outcome¿ in your study by using scientific scale, and make a comparison according to the definition.

We used a simple definition for poor outcome i.e. children who died or had neurological sequelae at discharge were defined to have had a poor outcome ¿ data management section, page 8. The diagnosis in patients with such poor outcomes is now included as table 4.

5. Lines 1-2 from the bottom, last paragraph in the Method section on Page 7, in my opinion, only p value<0.05 at univariate were included in the stepwise logistic regression model.

We agree. This has been corrected (page 8).

Result section:

6. The result section should be described more detailed. There are many data missing, including the timing of seizure (immediate after hospitalization or seizure after hospitalization), and the duration of seizure.

The main aim of this report was to estimate the incidence, etiology and outcome of acute seizures in children admitted to hospital. A detailed description of the seizure semiology and characteristics as above will in future be the subject of a different paper.

7. Please describe the etiologies of death among seizure patients in text. Were all of them caused by the complications of seizure or the severity of infection? In my opinion, seizure is one of the clinical features in the critically ill patients after infection rather than the major cause of mortality or morbidity.

The etiological diagnosis in children who died is now described in the text (immediate outcome, page 12) and a table of the diagnoses in patients with poor outcome has been provided (now table 4). Although we agree that most deaths were due to the severe underlying disease (coma, severe acidosis,
hypoglycemia, bacteremia and infections in neonates (pages 13 and 16) rather than the seizures, status epilepticus contributed to some deaths especially in patients with malaria.

8. Please add the mean duration of hospitalization in those patients with or without seizure.

We have provided the median duration of hospital stay (data is skewed) for the two groups of patients. This now forms the first sentence under immediate outcome (page 12).

9. Page 10 and 11, in the Result section, the exact numbers of causative pathogens of bacteremia and bacterial meningitis should be described in detail in the text or in the footnote of Table 3. By the way, *viridians streptococci* is a group of streptococci, and should not be italic.

These have been provided in the text on pages 11 and 12.

10. Last paragraph of the Result section on Page 12, authors should use scientific scale to evaluate the therapeutic outcome, especially in the neonatal group.

Again as in 4 above, outcome was defined in terms of death or survival and among survivors it was based on the presence of gross neurological deficits. This has been described in the data analysis section and under outcome.

Discussion section

11. Discussion should be rewritten according to the result of your study.

Appropriate changes to the discussion have been made.

Reviewer 2

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1. Providing outcomes data and risk factor assessment for the combined (lumped) group of all children presenting with acute seizures really doesn’t provide much information to clinicians or epidemiologists when the lumped group of acute seizures includes such diverse conditions as cerebral malaria, febrile seizures and meningitis. Clearly defining etiological sub-groups and then providing risk factors for and outcomes among those clearly defined sub-groups would be much more interesting and valuable data.

We created a new table (now table 4) under immediate outcome to describe the outcomes of the different causes of seizures. It clearly stands out that seizures associated with respiratory tract infections and possibly acute diarrheal illnesses are fairly benign while those due to malaria (may be influenced by level of consciousness at presentation), meningitis, birth asphyxia etc are associated with increased mortality or neuronal damage. This strengthens the earlier descriptions in the paper. Additional discussion is provided in the discussion section under outcome, page 17.
2. Data presented represents the incidence of seizures presenting for care in the region, not the incidence of acute seizures in the region. Although the study team has a defined patient base, it would be erroneous to assume that all (or even most) children with acute, fever-associated seizures present for care. The fact that this study found incidence rates for acute seizure highest in populations living near the hospital further supports this reality. Therefore, all statements re: the incidence rates reported in the paper need to reflect that it only provides incident data for those children presenting to a hospital for care. Although buried in the discussion the authors acknowledge that their estimate is an "absolute minimum," the limitations of the data in this regard aren't evident on a casual review of the abstract or paper.

We acknowledge this limitation and have revised the abstract to reflect this fact. The fact that not all children with seizures do present to hospital has been acknowledged in the methods section and the discussion on this limitation has been expanded.

3. Was any standardized data collection instrument used for this work, or was data ascertained as part of routine care and then extraction of data elements from the usual medical record was conducted later? If a standardized intake form or assessment was completed, please provide that form for review. If no such standardized data was routinely collected prospectively as part of the study, can one assume that anything "not documented" was assumed to be absent (e.g., family history of epilepsy)? Providing the "not documented" rate for data elements included in the analysis is needed.

Yes, a standardized data collection instrument was used. In Kilifi hospital, all clinical data for patients is electronically entered at admission and only after completion of all the fields can the clinician proceed to print hard copies. At the onset of the study, this system was modified so as to collect additional parameters important for this study (files attached for reviewers). A positive history of seizures prompted the clinician to enter data on seizures such as previous episodes region of onset, type, duration, and family history, and at discharge clinicians completed forms on the outcome and types of neurological deficits if present.

4. Precisely how was "malaria" as a primary diagnosis defined in this work? How do children with "malaria as the primary diagnosis" differ from children with a positive malaria slide? How was this clinical distinction made? This is particularly problematic since without funduscopic confirmation of malarial retinopathy, the diagnosis of "clinical malaria" invariably includes a number of children with incidental parasitemia plus another etiology for seizure. The authors conclude that the most common cause of acute seizures in this study was malaria, but no clear operational definition of malaria is provided. Since asymptomatic parasitemia is common in this region, this is an important issue.

Children with "malaria as a primary diagnosis" had asexual forms of P. falciparum parasites detected on blood films with malaria as the only or main diagnosis. Children with malaria parasitemia but admitted due to other clinical
diseases e.g. acute trauma, cardiovascular disease were deemed to have other primary diagnosis. We acknowledge that this definition may be imprecise. Although the presence of features of malaria retinopathy on indirect ophthalmoscopy may improve the diagnosis of malaria in children with coma, the procedure is rather difficult to perform in conscious but sick and often irritable children who formed the majority of this group. The majority of children with coma however had this procedure performed.

5. Table 1 needs to include data on parasitemia, particularly since malaria is reported to be the commonest cause of acute seizures in this study.
This has been added.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

6. Was HIV status assessed at all? What role, if any, did HIV-related illness play in the cases and comparison patients in this work?
Until October 2006 (the last month of the study period), only children with probable HIV infection were tested for HIV infection as part of a diagnostic testing and counseling program. Since November 2006, all admitted children were tested for HIV. From November 2006, all pediatric admissions receive HIV testing. The results show that 8% are HIV infected. We however do not have ethical approval to link the sets of data to individual patients to answer this question since our initial protocol did not request for this. This limitation has now been included in the discussion on page 16-17.

7. ¿Fewer children with seizures were severely wasted¿
What do the authors attribute this to? Less severe malaria among the wasted? Bias in who parents bring to hospital?
It is not clear from this association study what the reasons for this finding may be.

Sincerely

Richard Idro