Author's response to reviews

Title: HIV Prevalence in Severely Malnourished Children Admitted to Nutrition Rehabilitation Units in Malawi: Geographical & Seasonal Variations A cross-sectional study

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Version: 2 Date: 18 January 2008

Author's response to reviews:

Dear Sirs

Thank you very much for your valuable comments received in relation to the article HIV Prevalence in Severely Malnourished Children Admitted to Nutrition Rehabilitation Units in Malawi: Geographical & Seasonal Variations A cross-sectional study. Please find below responses to your comments and attached an updated version of the paper

Best wishes

Susan A Thurstans, Marko Kerac, Kenneth Maleta, Theresa W Banda, and Anne Nesbitt

Reviewer 1. Stephen SM Graham

Responses to reviewer's report (in italic text)

General

This is an important study as surprisingly few studies have looked at the prevalence of HIV in severely malnourished children in an African region where both diseases are endemic in children - and none in a number of different, relevant settings comparing region, season and urban to rural. Options for paediatric HIV care have improved considerably in the last few years and HIV is a major cause of poor response to nutritional rehabilitation in severely malnourished children.

Methodology is sound. Data are not overinterpreted and limitations are acknowledged.
Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

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

1. It would be useful to add data, if available, on HIV prevalence broken down by type of malnutrition eg oedematous malnutrition versus marasmus, and by age.
   Please see the table 2
2. The three tables could readily be combined into one table.
   This has been changed in the paper
3. Reference to Kessler et al is listed twice
   This has been deleted

Discretionary Revisions (which the author can choose to ignore)

What next?: Accept after minor essential revisions
Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:
I declare that I have no competing interests

Reviewer 2. John Aberle-Grasse
Responses to reviewer’s report (in italics)

General

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

1. Problem with sampling. If the results are to be regionally representative, the sample size was calculated for region as described in methods. It looks to be a nested sampling frame with 4 sites per region; site selection within region should be randomized accounting for representation classes: main regional referral center, urban, rural. Otherwise the sample is not going to be representative of the
region. If this was done it should be described. Also the rationale for the nest classes should be defended.

We are open about and acknowledge our limitations in the paper ‘limitations’ and ‘methodology’ sections. Our study size was constrained by limitations of resources, hence we are cautious in our comparisons and analyze as a factorial design i.e. rural versus urban; wet versus dry season only. We do not attempt to say for instance anything about rural versus urban nested within the rainy/dry season.

We also note that our NRU prevalence figures reflect national adult prevalence figures. These are done on larger numbers and a tighter methodology. Our consistency with these figures strengthens the case for our findings being valid.

2. Methods section state sample needed was 200 children per region per season: 200children x 3 regions x 2seasons = 1,200 total.

This interpretation of the statistics is incorrect. Ours is a factorial type study and the stats section has been modified to clarify and avoid future misunderstandings by showing that the sample sizes we achieved are in fact adequate for the comparisons made.

Page 8 Results show total of 570 children across all regions and seasons. As such the study does not follow the methods for sampling. Either methods should be modified or results should explain this difference. We hope that this has now been done to the reviewer’s satisfaction. Hence, the difference between prevalence in north and south region is not significant because sample is too small. Please see revised methods section. The North-central and South-Central comparisons ARE both valid and significant. The North-South comparison is non significant according to the criteria we have described. Any differences are likely to be statistically ‘significant’ if the sample size is large enough. What matters more, we believe, is whether statistical significance relates to clinical/operational significance which we have described and chosen accordingly. Choosing tighter criteria with greater sample size may well have shown a ‘statistically significant’ N-S difference. However, we do not believe that the clinical/operational implications of this would have added important value to our overall interpretation and final messages. So that on page 12, Limitations, statement saying statistical differences in comparison groups were maintained is not accurate. This has been changed in the limitations section.

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

3. Page 7 Testing algorithm should be associated with standard country guidance. With discordant rapid tests, is Malawi MOH SOP to use PCR or
Western Blot or 3rd rapid test tie breaker.

Thank you this has been revised in the text to describe the national protocols

Discretionary Revisions (which the author can choose to ignore)
3. Page 6 What region was urban site with Child prev 34% since authors indicate in table that there is great range between regions.

This has been included the study took place in Blantyre in the southern region of Malawi

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions
Level of interest: An article of importance in its field
Quality of written English: Needs some language corrections before being published
Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.
Declaration of competing interests:
I declare that I have no competing interests

Reviewer 3: James Tumwine

Responses to reviewer’s report (in italics)
General

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)
This study is on interesting subject: HIV and severe malnutrition. However the focus is too narrow to be of much scientific merit.

The purpose of our study was to be of clinical benefit to patients through informing an important yet often still controversial area of public health / public policy: science serving policy rather than a goal in itself.

The focus is narrow because we wanted our science to be to-the-point. We had neither the intention nor the resources to present a comprehensive review of all issues related to HIV and malnutrition. This, we feel, is best done by a whole body of literature rather than one paper or one study alone. Our approach results in short, clear, and concise messages this is in no way the same thing as being too narrow to be of much scientific merit.

What the authors have done is to study the prevalence of HIV infection amongst
children admitted to the Nutrition rehabilitation units in Malawi without any significant focus. One is left with the nagging question: So what?

Our aim and focus was to quantify the magnitude and distribution of the problem at public health level. This we have done.

Firstly, the level of HIV in severely malnourished children at national level has not been previously documented. One of the many drivers for this study was to understand the wide variations in outcome from the different NRU’s: recovery rates were higher in many of the least well resourced rural NRU’s despite all the NRU’s at that time having access to the same protocols and the same feeds and drugs. Conversely, many large urban NRUs were constantly being questioned about poor outcomes without any knowledge of background HIV rates. Testing for HIV at that time was not easy to access even in tertiary centres and we needed to demonstrate the important role testing had to play in the understanding of and management of HIV in a high HIV prevalence area in the hope that funding for testing would be forthcoming. The concept of ‘new variant famine’ and the link of the food crisis with HIV were beginning to be acknowledged at a public health level Lancet 362 1234-1237 2003 but had not yet impacted on improvements in case management of malnutrition.

Secondly, our study adds important evidence to arguments about whether HIV testing is acceptable and should or should not be done routinely, especially in high prevalence areas. Since the current WHO manuals on the Management of Severe Acute Malnutrition (1999, 2003) are still minimalist on HIV (and even in 1999 advocate avoidance of testing), we feel our study makes an important contribution to forthcoming updates and revisions. This was a core argument we made to UNICEF who consequently approved and funded our work. It is also for this reason that we would want our study published in the open access literature. Thus, all can easily access and read - in full - our study report.

An analysis of epidemiological conducted by UNICEF and published in Public health Nutrition 8 (6) 551-563 2005 ‘AIDS, drought and malnutrition in Southern Africa’ stresses the importance of ‘expanded nutritional surveillance in monitoring and responding to deteriorating trends’ and discusses the shifting vulnerability to deteriorating nutritional status from children in rural to children in urban areas in the region. We feel this study despite its limitations attempts to explore some of these issues from an operational perspective particularly in respect of the high burden of HIV disease in urban NRU’s.

We would want readers and policy makers to make individual decisions about the validity of our study and implications for other settings. Even now, there are calls to avoid routine HIV testing (Ad Asante, Scaling up HIV prevention: why routine or mandatory testing is not feasible for sub Saharan Africa, bulletin of the world health organisation, August 2007, 85 (8)). Our study, in particular the high testing uptake adds important evidence to counter this viewpoint. Without testing availability, many patients will not be able to access ARV services that are now available or lobby for ARV scale up where services are not yet widely available or integrate nutrition, care and support with HIV and AIDS services.
They aimed at describing the burden and distribution of HIV infection among severely malnourished child in NRUs in Malawi.

Specific:
They had the opportunity to classify the malnutrition by presence or absence of oedema and to see whether this influenced HIV test result. The authors have also denied us access (if the information is available) to the WHO/CDC classification of the stage of HIV in these children. We are also denied information on presence of opportunistic infections and on the outcome of these children.

This was not the aim of the study so some of this data does not exist. As indicated previously, we felt that including too many such secondary outcomes would have distracted from our core messages and is best addressed by other studies designed specifically to address these other issues.

We have included a breakdown on the presence and absence of oedema but we do not have this information for all children.

It is not clear why children under the age of 15 months were excluded yet the authors had access to DNA PCR for distinguishing true infection from maternal antibodies.

Funding and logistical constraints to this study did not allow PCR on all children. PCR testing at the time was expensive, turnaround time long, and laboratory access restricted. We took external advice on this issue and ultimately came to the conclusion that we should not test <15m. Our ethical priority was to contribute to patient care as well as advancing science. As such, we had a responsibility to ensure that those who wanted results got them in a timely manner from their counsellors.. This was possible for a small number of patients who had indeterminate spot tests. It would not have been possible for each and every patient <15m had we chosen to include these.

Several studies have shown that CD4 cell percentages are important in the classification and subsequent management of HIV infected children especially those who are severely malnourished. It is not clear why CD4 percentages were not done. Resources were not available for this at the time and this was not the aim of the study.

At the end of the day, what proportion was referred for HIV care including anti retroviral drugs?

Antiretroviral therapy for children was very limited in availability at the time of this study .. During the second round in 2 of the centres ART became available. During the study all children and caretakers identified as being HIV positive were referred to the best available services in the area. This included PMTCT, HBC
and cotrimoxazole prophylaxis therapy.

Clinical and laboratory features of micronutrient deficiency are routinely sought in the assessment of severely malnourished child children. It is not clear whether this was done in this study and what happened to the results.

This was not the aim of the study and was not undertaken. All patients in this study were treated according to standard Malawi protocols, which include clinical assessment for micronutrient deficiencies (though in Malawi, isolated deficiencies are rare and all patients have vitamin A, and folate on admission to the NRU). Routine laboratory testing for micronutrient deficiency is not part of the Malawi SAM protocol neither is it part of WHO SAM management guidelines.

Statistical issues:

The sample size calculation for a prevalence survey is straightforward. The sample size is estimated by the formula: \( pqZ^2/d^2 \) where \( p \) is the prevalence and \( q \) is \( 100-p \); and is the precision or error acceptable and is usually set at 5%.

It is not clear why a power of 80% was used here since no comparisons were being made. Or if comparisons were being made, it is not clear what was being compared with what.

The text has been changed to clarify which comparisons were being made. These are central to this study and are comparisons between:
- rainy (hungry) season vs dry season
- rural vs urban
- southern vs central vs northern region

We have put the retrospective power calculations in the text of the paper for clarity and to address specific statistical concerns raised in the first review. However, as referees feel appropriate, these few sentence may be either left in or removed and used for their information only during peer review process.

Reference to the prevalence being higher amongst the boys is out of place since it could have occurred by chance.

This point has already been recognised by the statement “non-significantly higher in boys”, we are merely describing the findings rather than trying to imply that the difference was due to anything other than chance, however we have modified in the text.

The data management section lacks adequate detail. For example the authors talk about odds ratios being calculated using StatCalc utility. What were these calculations for?

These calculations are to calculate the odds ratios.
What was being compared with what?

This has been clarified again in the sample size section

And there more robust programmes for this type of data analysis (STATA, SPSS etc) that EPIinfo.

Statcalc is a standard element of the Epiinfo statistical package, designed and distributed as freeware by CDC, USA- an institution of international repute, whose outputs and programmes are used worldwide, regularly revised, updated, and widely respected. Epiinfo is widely used in nutrition and epidemiology studies. We do not thus agree with this referee's view that statcalc is insufficiently robust and that the same calculation needs to be repeated in another programme.

The presentation of the data in several small two by two tables is problematic. All the work could presented in just one table with the exposure variables in the rows and the outcome (HIV test result) in the column

We have combined the tables accordingly.

The authors make unsubstantiated statements such as Knowledge of underlying clinical infections contributing to SAM means

This has been changed to specify HIV and HIV associated infections

From the data presented we only have a glimpse of the HIV prevalence and that is all. We even do not have simple information as to what proportion of the children had for example: fever, diarrhea, cough, oedema, pallor of the mucous membranes, oral thrush etc. So there is really nothing clinical about this work.

Our main point is that ready access to HIV testing is needed by practising clinicians in high prevalence areas we never attempt to present this as a clinical work, however, it is highly relevant to clinical paediatrics in resource poor settings since it shows that HIV prevalence is high in NRUs. Clinical algorithms used in NRUs to determine who does and does not have HIV have poor sensitivity / specificity and hence are of little real-world value especially since now cheap HIV test kits are available and ARV availability means that not to test is to can deny access to treatment.

Yet such simple information is available even in the most rudimentary NRU.

No effort has been made to explain the key findings of this study: For example could religion and by proxy, the practice of circumcision, be a factor in the north south difference in the prevalence of HIV?

As predicted the findings reflect the national prevalence estimates. Some explanation of this has been added to the background section
Are the NRU based in similar institutions? Some I am sure would be based in referral centers such as teaching hospitals. One would expect those in referrals centers to possibly be more severe. If HIV care services were available in these centers they might attract more HIV infected children than the centers not offering specialist services and control for this in a logistic regression model.

At time of study, child ARVs were available at only one centre in the country, and then only in the second round of the study. Admissions to the NRUs even at the regional centres are from the surrounding district, the children are usually poor families who cannot afford to travel to other than the nearest NRU The whole reason for the study is to demonstrate such differences between the urban regional centres and others. Hence there is no need to `control¿ for the differences as suggested here. This needs better explanation am running out of steam!

References have been formatted with End Note programme using funny number (I, ix, vi etc) This needs to be changed please.

Sue can we move from Roman numerals or are we stuck with them for this journal!

Why is it that HIV prevalence is lower in the rainy/hungry season? No plausible explanation has been given. This has been added to text

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

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Discretionary Revisions (which the author can choose to ignore)

What next?: Reject because scientifically unsound

Level of interest: An article of insufficient interest to warrant publication in a scientific/medical journal

This study has already influenced policy in Malawi by encouraging wider HIV testing within the treatment of malnutrition. As a result more children with severe malnutrition and their caretakers are accessing ARVs. We believe the reason it should be published is to encourage others to do the same, it is a sad reality that in many places HIV and severe malnutrition are still viewed separately and services are not integrated. We would like this paper to advocate to other countries and additionally the World Health Organisation, for a change in policy to more HIV testing to be integrated in acute malnutrition guidelines. Preliminary presentation of this paper has been well received at meeting such as the international AIDS conference, College of medicine Malawi research meetings and National AIDS commission of Malawi meetings, and has been recognised as
a paper with a high level of scientific/policy interest and implication. We therefore believe this paper deserves journal publication to reach wider audience.

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 no competing interest