Author's response to reviews

Title: Factors associated with non-adherence to Artemisinin-based Combination Therapy (ACT) to malaria in a rural population from holoendemic region of western Kenya

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Author's response to reviews: see over
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The Editor
BMC Infectious Diseases

RE: Re-submission of manuscript ID MS 3443423660684289 entitled, ‘Factors associated with non-adherence to Artemisinin-based Combination Therapy (ACT) to malaria in a rural population from holoendemic region of western Kenya’

Dear Rose McGready:

We appreciate the thorough and prompt review of our work. We have made all the suggested changes in the manuscript. We have read through the comments and addressed them in a point-by-point fashion - indicated in the text of the revised version of our work (in red). It is with great pleasure that we re-submit this manuscript for consideration in BMC Infectious Diseases.

Response to reviewers’ comments

Reviewer's report:
This study aimed to evaluate ACT adherence level, factors associated with non-adherence and accessibility in households (n=297) in rural location of Southeast Alego location in Siaya County in western Kenya. The research question is well defined, the study has been carried out well and the paper is well written.

Major Compulsory Revisions

Comment 1: Since a complete list of all members of the population did not exist, sampling was carried out using multi-stage and probability proportion to size sampling methods. These methodologies may be appropriate, but they are not well described. This part should be re-written. More detail describing the study design would be helpful, notably the sample selection in the different stages. A figure may help to do it.

Response 1: We want to thank the reviewer for raising this very important observation and apologize for the oversight. We have now described the sampling process in great detail in the text to address this important point. The section now reads, ‘The divisions, locations, sub-locations and the villages formed the clusters. Siaya District has three divisions namely Karemo, Boro and Uranga divisions (according to the administrative boundaries at the time of the study) (Figure 1). Karemo division has five locations namely; Siaya Township, North Alego, East Alego, South Alego and Southeast Alego was selected as study units at the division level. Southeast Alego location, which has four sub-locations namely Masumbi, Nyang’oma Kogelo, Mur Ngiya and Bar Agulu was selected at the location level. The sample size was drawn from
all the four sub-locations of Southeast Alego location. The sub-locations had a total of forty two (42) villages. To ensure equal representation from each of the sub-locations and the villages, data on the number households in all the sub-locations and villages were obtained from Kenya Bureau of Statistics offices in Siaya District. The obtained data was then used in determining the proportionate sample size for each sub-location and village. This site was targeted for the study since it is one of the areas with highest malaria burden in the district. In addition, interventions such as stable supply of ACT were being implemented in this study area at the time of the study (Figure 1).

Comment 2: Due to the effects of clustering and unequal selection probabilities, it generally is not plausible to view the survey observations as independent and identically distributed. For that reason, it generally is not appropriate to analyze complex survey data with methods based on independent and identically distributed assumptions. The authors should consider performing design-based analysis of survey data.

Response 2: We thank the reviewer for raising this excellent point. We have now revised the Results section to take into account this important point and now it reads, ‘Consistently, logistic regression model demonstrated that low age (OR, 0.571, 95% CI, 0.360-0.905; P=0.017), higher education level (OR, 0.074; 95% CI 0.017-0.322; P<0.01), ability to read (OR, 0.285, 95% CI, 0.167-0.486; P<0.01) and higher income (Ksh.>9000; OR, 0.340; 95% CI, 0.167-0.694; P=0.003) were associated with ACT adherence (Tables 5-7). However, adherence was not significantly associated with gender, HH size, HH head, marital status, source of ACT and distance to the source (Tables 5-7).’

Comment 3: The paper does not contain a clear discussion of the limitations of the study, Point estimators could be biased under a complex design. I would consider that it might be worthy of some comments.

Response 3: Once more we thank the reviewer for raising this excellent point. A section has now been included in the manuscript discussing the study limitations and the section now reads, Study limitations
The study was based on both self-reported and medically-diagnosed episodes of malaria experienced in the previous two weeks prior to the interview. Hence, we could not verify the authenticity of the information obtained from the respondents. Secondly, the case-specific definition of malaria could not be ascertained in this study, since some sought to over-the-counter drugs when they had symptoms similar to those of malaria. Moreover, there was recall bias in this report. Participants were asked questions based on a two-week recall period. Some of the participants would therefore, not vividly remember whether they actually had malaria/fever or how they took the drugs in the last two weeks preceding the interview. To increase accuracy on duration of treatment, hospital cards were reviewed and the drug sachets observed and number of tablets remaining or taken were counted. This certainly affected the quality of this study. However, the two week recall period is the reference period used by WHO surveys and has been adopted by many researchers for similar surveys. Therefore, findings in this report are of comparable quality.
Similarly, structured interview-based studies are limited by the pre-determined responses, which are susceptible to response bias. However, attempts were made to minimize this potential source of bias by testing the tool, training field assistants in its administration, and amending it to make the wording familiar and culturally-appropriate.

Comment 4: Regression analyses were used to identify variables associated with adherence to ACT. Indeed, the authors show the results of these analyses by means of the regression coefficients (#) and p-values. Since the dependent covariate (adherence to ACT) seems to be binary (non/yes), logistic regression analyses would appear to be more appropriate. In addition, these results could be expressed in terms of odds ratios.

Response 4: We appreciate this important observation from the reviewer. We have performed a logistic regression and the data has now been presented as odds ratio (OR), 95% confidence interval (CI) and the P values. Part of the abstract now reads, 'Consistently, logistic regression model demonstrated that low age (OR, 0.571, 95% CI, 0.360-0.905; P=0.017), higher education level (OR, 0.074; 95% CI 0.017-0.322; P<0.01), ability to read (OR, 0.285, 95% CI, 0.167-0.486; P<0.01) and higher income (Ksh.>9000; OR, 0.340; 95% CI, 0.167-0.694; P=0.003) were associated with ACT adherence.' The section in the text under Results now reads, ‘Consistently, logistic regression model demonstrated that low age (OR, 0.571, 95% CI, 0.360-0.905; P=0.017), higher education level (OR, 0.074; 95% CI 0.017-0.322; P<0.01), ability to read (OR, 0.285, 95% CI, 0.167-0.486; P<0.01) and higher income (Ksh.>9000; OR, 0.340; 95% CI, 0.167-0.694; P=0.003) were associated with ACT adherence. However, adherence was not significantly associated with gender, HH size, HH head, marital status, source of ACT and distance to the source (Tables 5-7).’

Comment 5: Regarding the simple size calculation, the reader needs to know on which parameters the calculation was performed.

Response 5: We thank the reviewer for this valuable comment. We have endeavored to shed more light on how the sample size was calculated. The section on sample size determination now reads, “The sample size was based on Fisher’s formula for sample size estimation [Fisher L: Self-designing clinical trials. Statistics in Medicine 1998, 17:1551-1562] taking into account population size greater than 10,000 (i.e. a total of 17,780 people were resident in the study site at the time of the study). The formula for sample size determination used the prevalence of non-adherence to anti-malarial and this was estimated at 50% since the prevalence is not known”.

Minor Essential Revisions
Comment 6: References should follow the instructions of the journal.

Response 6: We thank the reviewer for raising this important issue that we overlooked. The references in the manuscript have now been formatted in endnote using the BMC Infectious Diseases style and now have the consecutive numbers in square brackets.

Comment 7: Figures 1 to 3 are not necessary.
Response 7: We thank the reviewer for raising this concern; we have now deleted figures 1 to 3 and explained them in the text as recommended in the current version of the manuscript.

Reviewer # 2

General Comments
I have many of the same questions about sampling as did the reviewers and the Associate Editor. I suspect this is mainly because of how the process is described in the paper. In addition, I have questions about the regression approach used to estimate the impact of different factors on adherence to ACT.

Major Compulsory Revisions

Comment 1: Study Participants, Sampling Design, Research Procedure, p 7-9. I struggled to understand how study participants were selected. It would help to rewrite the paragraph at the bottom of page 7 and at the top of page 8 in the actual order in which things were done. For example, how were the 388 households selected? How were clusters defined? What elements were included within each cluster, and how were those elements chosen? Information about the sampling procedure is repeated unnecessarily (p 8, middle paragraph and p 9, Research Procedure). Why was data collected from all 388 households if 297 were selected?

Response 1: We appreciate the reviewers comment on this section. This section on the study participants and sampling design has been re-written to avoid the unnecessary repetitions. Secondly, although data was collected from 388 households (individuals, since one individual per household was interviewed) who had recent incidence of malaria and used anti-malarial drugs, only 297 used ACT to treat malaria. Hence, only this sample (297) was included in the analyses assessing adherence to ACT.

Comment 2: Statistical analyses, p 10. How was level of adherence to ACT estimated from duration of treatment and number of tablets taken? Was adherence considered to be a binary [yes-no] response? Was multiple linear regressions used to estimate level of adherence, or was logistic regression done to estimate the probability of adherence? From Figure 3, it appears that adherence was considered to be a binary response. Was logistic regression used? In the second-to-last line of this section, chi-square analyses were done to analyze proportions. How does one analyze something thematically? Does that mean qualitatively?

Response 2: Once more we want to thank the reviewer for such an excellent observation. In the context of this study, adherence was treated as a binary response of [yes-no] at the individual study participant’s level. In light of this, linear regression was initially performed and currently we have extended the analyses and performed multiple logistic regressions. This is now presented as odds ratio (OR and 95% CI). In the context of the current study, the level of adherence was used to mean the proportion of the total population that adhered to ACT i.e. 47% adhered and 53% were non-adherent, as determined through the chi-square tests. Thematic analysis is one of the most commonly used methods of qualitative analysis. Qualitative data can be organized into themes depending on the responses from the respondents. It involves
searching through data to identify any recurrent patterns. A theme is a cluster of linked categories conveying similar meanings and usually emerges through the inductive analytic process which characterizes the qualitative paradigm. In our case, qualitative data on possible causes of adherence from the KIIIs were organized into relevant themes such as socio-economic, demographic and environmental factors.

**Minor Essential Revisions**

**Comment 3:** Throughout the paper. P values greater than 0.01 can be rounded to the nearest 0.01. Percentages can be rounded to the nearest integer.

**Response 3:** We thank the reviewer for raising this important point. This has been corrected. The $P$ values of “$<0.001$” have now been rounded off to “$<0.01$”

**Comment 4:** Figures 1-3. The information in these Figures can be better presented in a simple table or even within the text itself.

**Response 4:** We thank the reviewer for raising this concern, we have now deleted figures 1 to 3 as recommended and the data presented only in the text in the current version of the manuscript.

If you have any further comments and/or suggestions, we would be happy to address these concerns.

With highest regards,

Prof. Collins Ouma, PhD