Author's response to reviews

Title: Effect of a multi-faceted quality improvement intervention on inappropriate antibiotic use in children with non-bloody diarrhoea admitted to district hospitals in Kenya.

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Author's response to reviews: see over
Dear BMC Editors,

Effect of a multi-faceted quality improvement intervention on inappropriate antibiotic use in children with non-bloody diarrhoea admitted to district hospitals in Kenya – MS: 96460375394982

Thank you for your feedback on our manuscript. Our responses to editorial and reviewers’ comments follow.

1. Editorial comments:
   a. “We recommend that you ask a native English speaking colleague to help you copyedit the paper.”

   Co-authors Elizabeth Allen, James Carpenter and Mike English who are native English speakers have edited the manuscript and suggested specific improvements which are included in this version.

   b. “Experimental research that is reported in the manuscript must have been performed with the approval of an appropriate ethics committee. Research carried out on humans must be in compliance with the Helsinki Declaration (http://www.wma.net/e/policy/b3.htm), and any experimental research on animals must follow internationally recognized guidelines. A statement to this effect must appear in the Methods section of the manuscript, including the name of the body which gave approval, with a reference number where appropriate.”

   This study was conducted with the approval of an ethics committee. The following text has been inserted into the ‘Methods’ section: “Ethical approval for the trial was granted by Kenya Medical Research Institute National Ethics and Scientific review committees (SSC No. 991).”

   c. “Please remove the keywords, word count and box from your title page and instead include email addresses for all the authors, as well as that of the corresponding author.”

   The keywords, word count and box have been removed from the title page; the authors’ email addresses have been included.

2. Reviewer 1 comments: none

3. Reviewer 2 comments:
a. “Figure 5 is missing.”

Figure 5 was provided in the initial submission and has been resubmitted in this revision.

b. “A comparison with other studies concerning intervention to improve appropriate use of antibiotics should be made. In particular, the Cochrane systematic review by Peter Davey et al. should be made”

We appreciate the suggestion but on reflection feel that a comparison to the Davey et al. review is not the most appropriate because the outcomes considered (microbiological outcomes) are very different from the ones we have analysed. We hope the editors will agree that a more appropriate systematic review to draw on is that of Grimshaw et al. that focuses on clinician behaviour, a review now discussed in the ‘Discussion’ section.

c. “I think it may be useful to report the number of children with non-bloody diarrhoea by hospital. Looking at figure 4 I guess that in some hospitals the number of children is low.”

The number of children with non-bloody diarrhoea by hospital has been reported. The words “(median across hospital 147.5, range 53–227)” have been added in the ‘Data’ section under ‘Eligible sample’, next to the number of children with non-bloody diarrhoea.

4. Reviewer 3 comments:

a. “The training of Full intervention group was for 5.5 days and partial intervention group had training for 1.5 days, what were the differences in the contents of two groups?”

“Number of groups the staff (30-34 in full intervention group and 35-40 in partial intervention group) were trained?”

“Number of recommended practice discussed during the training in each group?”

“What were the contents of face-to-face feedback?”

“The supervision was 2-3 monthly and face-to-face feedback was 6-monthly, what was the purpose of the two supervisions and how the supervision data (information) used? What data (information) was collected in each supervision?”

While we have expanded descriptions to address these points, full and detailed description of the intervention would require further text; we are happy to provide this detail if the editors feel it is necessary and will approve the expanded word count. At present, to keep within recommended word-count limits we have instead pointed the reader to published work describing the intervention. These references are provided in the ‘Methods’ section under ‘The intervention’. They include:


b. “The result shows that there were 1,160 children with non-bloody diarrhoea not needing antibiotics, however there were co-morbid conditions needing antibiotics. What % of co-morbid conditions needed antibiotics? The figure-2 shows the list of co-morbid symptoms and signs and not the diagnosis that the children suffered from? How the use of an antibiotic was decided appropriate in a child with non-bloody diarrhoea and a symptom/sign?”

The absolute number and proportion of children with co-morbid conditions requiring antibiotics has been stated in the ‘Data’ section under ‘Eligible sample’: “Of these 5,358 (56.6%) children had diagnoses requiring antibiotic therapy according to guideline recommendations.” Diagnoses, rather than clinical signs/symptoms, were the determinants of appropriateness of antibiotic use as stated above. Figure 2 has been retained in the manuscript because it effectively illustrates the diversity of symptoms examined for an association with the outcome.

c. “If a child with non-bloody diarrhoea and a co-morbid condition was treated with an antibiotic or antibiotics, was it taken as appropriate or inappropriate if an antibiotic was not complying or adherence to the national guidelines?”

The focus of this analysis was not the correctness of antibiotic use when antibiotics were indicated – such a child was excluded from the study population. The outcome of interest is inappropriate use of antibiotics in children with non-bloody diarrhoea. No further consideration was made of children who required antibiotics for any other condition. This is described in the ‘Data’ section under ‘Eligible sample’.

d. “The objective of the study is not clearly defined and partly it is incorporated in the ‘Method’. The first few sentences in the ‘Setting’ may be taken into the ‘Background’”

An ‘Objective’ section has been created and the first sentences in ‘Setting’ moved there. It now reads: “This trial was undertaken between 2006 and 2009 with the main end-point in 2008. It investigated whether an intervention comprising training health workers on the use of evidence-based guidelines for paediatric care, local facilitation, and external supervision and feedback, would improve the quality of care given to children with specific diagnoses admitted to Kenya's district hospitals.[17] In this paper we explore associations between the intervention and evidence for inappropriate antibiotic use in cases of non-bloody diarrhoea. This outcome was not a pre-specified trial endpoint.”

e. “What does unique ID number in the ‘Data’ mean? What does an identifier for the clinician in the ‘Data’ mean?”

This section has been reworded for more clarity as to the meaning and purpose of these ID numbers. It now reads: “Each record was assigned a unique ID number linking to a hospital and survey, and another ID number for the attending clinician linking to clinicians' characteristics.”

f. “How many data collectors were there in the study. What was the content of the three weeks training to data collectors?”
The ‘Data collection procedures and tools’ section has been reworded to indicate that there were four data collectors per team. The content of the training to data collectors has also been appropriately referenced (English M, Ntoburi S, Wagai J et al. An intervention to improve paediatric and newborn care in Kenyan district hospitals: understanding the context. Implement Sci 2009; 4: 42.).

g. “The ‘figures’ are not labelled.”

Labels for the figures are included in the main manuscript text file rather than within the figure image files as instructed.

h. “How was clinician defined in the study?”

Clinicians in this context were medical and clinical officers providing paediatric care. This definition has been provided in the ‘Methods’ section under ‘The intervention’. The word ‘clinicians’ has been replaced with ‘medical and clinical officers providing paediatric care referred to here as ‘clinicians’’.

i. “What could be the possible cause of a clinician admitting one child or 27 children in 24 months?”

There are several reasons for this. First, only a random sample of records were studied; second, admission events from night-time and weekends when ‘covering’ clinicians operate from other departments provide care; and thirdly because clinicians operated on a rotational basis spending varying durations in the paediatric department; some only provided on-call cover for short periods unlike others who were assigned full-time to the paediatric unit. These, along with other contextual issues, are explained in detail in references 18-21.

5. Reviewer 4 comments:
   a. Abstract
      i. “Concerning ‘main study end-points: the authors should state in the abstract that the outcome ‘inappropriate antibiotics use’ was not a prespecified trial endpoint, because this fact is an important while assessing the results.”

      We have added a line at the end of ‘Background’ in the abstract stating that this outcome was not a pre-specified end-point of the main trial.

      ii. “I wonder if ‘endpoint’ is really the appropriate term in this context. I consider it as confusing for the reader if aspects of the main study and the here shown results are mixed? The authors should focus in the results shown here (antibiotic use is rather an outcome than an endpoint), only on the aspects of antibiotic use and include some more aspects about the main study in the methods.”

      According to the CONSORT Statement ‘endpoint’ and ‘outcome’ can be used interchangeably in reference to the outcome variable of interest in a trial. Nevertheless to improve clarity the word ‘end-points’ has been replaced with ‘outcome’ in the ‘Results’ section of the abstract. All other uses of the word in the text are in reference to the main trial and have been retained.

      iii. “The authors should explain their study design in the abstract in more detail (including also ‘partial interventions’ used in the control)”
The study was a cluster-randomised controlled trial as indicated in the ‘Methods’ section of the abstract. The words ‘face-to-face’ and ‘didactic’ have been added to characterise feedback and training given to the intervention group vis-à-vis the control group to highlight the ‘partial intervention’. We believe that this text concisely describes the study design while keeping the abstract within the required word limit. We are open to expanding the abstract if the editors feel it necessary.

iv. “A few important patient and setting characteristics should be added in the abstract”

A brief description of the patient population has been included in the ‘Methods’ section of the abstract: “…7-day to 5 year-old children with acute non-bloody diarrhoea”. The most important setting characteristic for the abstract is the fact that the study has been conducted in a low-income setting – this is stated in the ‘Background’ section of the abstract. We have cross-checked this information against the CONSORT Statement and found that our description of these characteristics is sufficient.

v. “The authors should state that additional requirements for antibiotic use had been taken into account before deciding about inappropriate antibiotic use. Otherwise it will lead to misunderstanding that only diarrhoea was considered”

Text has been inserted in the ‘Background’ section stating that co-morbidities requiring antibiotic therapy were considered in defining (in)appropriate antibiotic use. Further changes to the abstract made in response to other reviewers’ comments have also clarified the eligibility criteria for the patient population studied.

vi. “Why did the authors not provide the absolute numbers of the primary outcome (prevalence of irrational antibiotic use in the intervention and in the control group)? This would be very helpful to assess the results in addition to the given odds ratio”

The numbers of children receiving antibiotics inappropriately in the two groups has been added to the ‘Results’ section of the abstract: “…313 of these being in the intervention hospitals vs. 437 in the controls.”

b. Background

i. “The authors should add some clinical data from literature explaining why the simple (but practical particularly for non-developed countries) distinction into bloody and non-bloody diarrhoea without considering further clinical aspects is an appropriate procedure. They should state what are the main pathogenic agents causing bloody diarrhoea in the setting addressed by the study.”

The following text has been added to the ‘Background’ section: “This is a pragmatic approach informed by the observation that most non-bloody diarrhoea episodes in the under-5 age group in low-income settings are self-limiting and caused by pathogens not susceptible (e.g. rotavirus, astrovirus and enteric adenovirus) to antibiotic therapy or for which antibiotics are likely of little value or even deleterious (e.g. salmonellae and campylobacter).[9] In contrast a significant proportion of episodes of bloody diarrhoea caused by shigella are
associated with considerable mortality and are ameliorated by antibiotic therapy.[10] Furthermore correcting dehydration is clinically more important due to its association with adverse outcomes.” References have been updated subsequently.

ii. “The authors should give some more information about some details of the main study in this paragraph (e.g. how was ‘quality of inpatient care’ defined)?”

The words ‘quality of inpatient care’ have been replaced with ‘inpatient paediatric care practices’ which is more specific. We have also provided a reference to the main study where more definitions are provided.

c. Methods

i. “I wonder if the ‘partial intervention’ in the control group was typical for the setting. If not, it seems rather a comparison of a ‘small’ to a ‘big’ intervention than a comparison to a control. A procedure of routine care cannot be declared unethical before an additional effect of an intervention was not proven to be clinically relevant. The authors should clarify this.”

The ‘partial intervention’ was not typical of this setting; it was better than support that should routinely have been provided by the Ministry of Health. The trial was indeed a comparison between a full multifaceted intervention and a partial one. The Ayieko et al. paper [18] clarifies this.

ii. “The authors should provide some information about the economic impact of the interventions. The strategies in the intervention groups seem to be rather cost-intensive and I wonder if they can be practically used in routine patient care in non-developing countries limiting the generalizability of this study.”

We are in the process of submitting for publication a cost-effectiveness analysis of this intervention A brief comment on its economic impact is however provided in the conclusion.

iii. “The authors should provide detailed information on how far the intervention concept, which was designed for other study endpoints of a main study, addressed the aim of the study shown here.”

The main endpoints in the original trial design focused on what we had reason to believe would be common clinical conditions. We also hoped the intervention would improve management of other conditions as it covered the eight top causes of childhood morbidity and mortality in our setting. Inappropriate antibiotic use was not a pre-specified outcome because we were not certain of the frequency with which it would be observed. This is therefore a secondary analysis, as acknowledged in the discussion, and importantly, an opportunity to develop alternative methods of analysis. We have provided descriptions of elements of the intervention that are relevant to this outcome, specifically (at the end of the ‘Methods’ section under ‘The intervention’): “Recommended practice for managing non-bloody diarrhoea included detailed history-taking, assessment for shock and dehydration, classification of severity of dehydration and appropriate rehydration therapy. The use of antibiotics was actively discouraged. This management plan was summarised in the form of clinical protocols provided
within guideline booklets for clinicians and nurses and wall charts and promoted during feedback and supervision visits.”

iv. “The sentence ‘the primary endpoint was the 3rd follow-up survey’ sounds confusing and should be modified (what was actually assessed as the primary endpoint?)”

The sentence has been modified to: “The primary outcome – inappropriate prescription of antibiotics to children with non-bloody diarrhoea – was measured at the 3rd follow-up survey.”

v. “As I understand the study design a positive ethic vote is mandatory. The authors should state that an ethic committee was involved for ethical reasons or give detailed information why it should not be necessary.”

Ethical approval for the trial was granted by Kenya Medical Research Institute National Ethics and Scientific review committees. This has been stated in the ‘Methods’ section.

vi. “The interventions should not only address the use of antibiotics but also rehydration and hygiene aspects. Were those aspects addressed by the intervention?”

Rehydration as part of recommended treatment for diarrhoea was promoted in the intervention; this is stated in ‘Methods’ under ‘The intervention’: “Recommended practice for managing non-bloody diarrhoea included detailed history-taking, assessment for shock and dehydration, and treatment with intravenous and oral fluids. The use of antibiotics was also actively discouraged.” Hand-washing with soap and water were also promoted in the wider context of the overall intervention, and the appropriate use of intravenous fluids was a primary outcome. These are described in related papers (references 17-23).

vii. “The authors described that only complete case-records were included. However in an intention-to-treat analysis all case-records should be included (e.g. with a worse-case scenario). If only completed records have been included, this can cause substantial bias. Authors should consider this point in the discussion.”

The ‘intention-to-treat’ principle was adhered to as all cases within a hospital were considered to have received the group treatment they had been allocated to. However where key data on an individual case are missing these cannot be included in an ITT (or per protocol) analysis unless the missing data is imputed. Thus individuals with missing data are a form of loss to follow-up and not a corruption of the ITT principle. Issues surrounding missing data are discussed in the first paragraph of ‘Limitations’ section including the potential for bias arising due to missingness.

d. Results

i. “Figure 2 seems difficult to read. I would recommend putting the data rather in a table. Authors should avoid using different intensities of grey which can hardly be distinguished from each other.”

We feel figure 2 is quite helpful because it illustrates the relative prevalence of clinical signs more effectively than a table would. Other reviewers did not raise
any objections to it. To make it clearer we have improved the contrast. We leave
the final decision as to whether it should be retained to the editors.

ii. “Figure 4 shows large differences especially in the control hospitals group (grey).
Sometimes the fluctuations in controls have an even larger extent than the effects
on the intervention group or the baseline level in controls is lower than the effect
in the intervention. This seems to limit the clinical relevance of the data, even if
statistical methods might show significance. The authors should discuss those
aspects or explain in the paper why those results can clearly prove an effect when
comparing intervention to control group.”

In a statistical sense these differences/fluctuations within each group only
contribute to the uncertainty about the estimate of the group effect. If, having
adjusted for other differences between the groups, e.g. baseline level, there is still
a difference in estimates of group effect over and above those introduced by such
uncertainty, then it is reasonable to claim that a ‘statistically significant’
intervention effect has been observed; this is the role of a rigorous statistical
analysis such as has been presented here. These variations do not limit clinical
relevance but, with the confidence intervals, provide further context for better
interpretation of the results. We agree with the reviewer that secondary analyses
require cautious interpretation.

e. Discussion

i. “The paper addresses a lot of statistical aspects. Beyond question, using
appropriate statistical methods is an essential part of a study. However,
particularly in the discussion the authors set a strong focus in statistical questions
while on the other hand delivering only rare clinical aspects. In my opinion, the
authors should include more clinical considerations and literature dealing with
those aspects (such as strategies to improve clinical guideline adherence). This
would make the data more interesting for readers with clinical background.

We have addressed, in a bit more depth, the relevance of the intervention to our
setting at the end of the first paragraph of the discussion: “This outcome is
relevant to our setting because childhood diarrhoea and dehydration are leading
causes of death, and contemporary evidence favours effective supportive
treatments such as rehydration while discouraging antibiotic therapy except in
cases of dysentery.[9] Furthermore inappropriate use of antibiotics is a waste of
important resources that a low-income country can ill afford.” We have also
attempted to explain why we cannot compare this to similar studies:
“Nevertheless this, along with other results of the trial [17], represents the first
evaluation of a complex intervention in our setting and evidence that it promotes
good paediatric care practice.” The need by some readers for more clinical
considerations than provided is appreciated but word-count requirements limit the
extent to which this can be done; we would be happy to provide even more details
if the editors feel it necessary. While we appreciate the need for a paper that
interests a variety of audiences we also feel that clinicians will need to be
introduced to an increasing array of statistical approaches suitable for evaluating
the impact of interventions in complex settings and this is one main aim of the
manuscript.

Additionally one have to state, that although statistical analysis is broadly
discussed, the strongest limitations of this study lay in this area: only small
number of included hospitals, lack of a control group offering only ‘usual’
support (without any additional intervention), and missing data (as mentioned by the authors).

Few studies in our setting deal with the hospital as a unit of intervention yet in reality this is how interventions are delivered. While it is true that the small number of hospitals in this trial is a challenge hard to address it is also true that there are considerable problems in trying to extrapolate results from individually randomised controlled trials or trials in small primary healthcare clinics to hospitals. So while these data throw up statistical challenges they are the best available from hospital settings in a low income country.

ii. “It would be more interesting to get an impression whether the results shown in this study are comparable to other similar surveys and what clinical consequences may result, if they can be generalized to other settings (e.g. also in so called developed countries, where missing guideline adherence is also a great drug-related problem).”

We have referenced the Grimshaw et. al. review which synthesised evidence for the use of guidelines in improving processes and outcomes of care, and commented on the similarities between their results and those presented here. The published results of the main trial from which these data are derived (highlighted in the discussion) are also consistent with these results.

“The authors should discuss the potential risk of false treated patients. E.g. is it relevant if patients were not treated with antibiotics in case they have no bloody diarrhoea but antibiotics were necessary or in case antibiotics were given in patients with bloody diarrhoea but (the chosen antibiotics) were contraindicated (e.g. what is about Clostridium difficile infections)?”

Excess morbidity and/or mortality might result from incorrect use of antibiotics when they are indicated; however discussing this in useful detail would significantly extend the length of this manuscript. We would prefer instead to focus on whether or not there was evidence of intervention effect. Furthermore ascertaining the need for antibiotics (e.g. using culture and sensitivity tests to identify microbes and determine which antibiotics to use) is beyond the scope of this work because these procedures were not carried out as part of our trial.

iii. “In conclusions and recommendations for further work I could expect some considerations about the generalizability of the intervention particularly when considering their costs. Here, the authors should only relay on facts proven by their results.”

As stated in the conclusions these findings complement those of the main trial indicating wider intervention effect than suggested in that analysis and potential generalisability to other diseases. We have also included a comment on preliminary results of an ongoing cost-effectiveness analysis of this trial and included a reference: “This indicates wider benefits of the intervention than suggested in the main study results implying that the intervention effects may be cut across diseases. Other ongoing analyses of the intervention suggest that it requires modest cost investments for comparatively substantial improvements in quality of care”. This type of intervention (guidelines, training and feedback) delivered at hospital level has not been tested in an RCT in our setting, and so far
we have relied on evidence from developed countries (where RCTs have not been used either) or extrapolation from other settings.

6. Reviewer 5 comments:
   a. “The present study is ill-planned. None of the ingredients (objective, method, analysis and result) of an epidemiological study is presented in a proper manner. Even the abstract has not elaborated on the main findings. The written language makes the contents incomprehensible at many places”

   We appreciate this comment but wish to point out that none of the other four reviewers made this assertion. The study report includes an introduction (background), detailed description of methods including analysis, results, discussion and a conclusion with recommendation for further work consistent with the recommendations in the CONSORT Statement. Following specific comments from other reviewers various sections, including the abstract, have been improved to include additional important details. The written language has also been improved upon by our native English speaking co-authors.

   b. “Setting: here the subjects (1,160 non-bloody diarrhoea children) are selected retrospectively from hospital records. The intervention is given to health workers, whom are studied prospectively. This fact should have been written exclusively”

   The study, like all randomised controlled trials, has been conducted prospectively but data collected on individual cases was obtained by chart review of retrieved files. This has now been clarified in the ‘Data collection procedures and tools’ section: “During each survey records of patients admitted to hospital on a set of random dates within the preceding six months (generated using Stata™) were selected with the aim of obtaining 400 records per hospital per survey. Each record was assigned a unique ID number linking them to a hospital and survey, and another ID number for the attending clinician linking each case record to clinicians' characteristics. Data were collected using a patient case-record data abstraction form.”

   c. “Objective: the primary objective is to study the effect of intervention given to health workers. This is not mentioned anywhere in straight forward terms.”

   The objective of the study is now presented clearly in the ‘objective’ section: “It investigated whether an intervention delivered at the hospital level comprising training health workers on the use of evidence-based guidelines for paediatric care, local facilitation, and external supervision and feedback, would improve the quality of care given to children with specific diagnoses admitted to Kenya’s district hospitals.”

   d. “Analysis: the authors are trying to use multi-level model, in which some variables are measured on individual level and some variables are measured on cluster (hospital) level. This is as simple as that. But they have described the analysis and results in such a complicated manner that one gets lost in reading the results and can not make anything out of that. There is no need to describe the model separately in an appendix. Multi-level models are well known. A proper reference would serve the purpose. At the most, they could have given the equation of the model used.”

   We appreciate that multi-level models are well known to statisticians but feel that it is useful to provide a detailed description of the model to explain, for those interested and from a more general audience such as that of a paediatric journal, how we arrived at our estimation of the adjusted intervention effect. Most regression models (including multilevel models) have a coefficient for the group effect (control vs. intervention) as the
estimated intervention effect. However in this study there is the additional effect of time to be adjusted for, and possible interaction between time and group effect. We investigated this and showed that the best estimate of the intervention effect is the coefficient for group-time interaction. The coefficient for group effect here is simply a comparison of the groups at baseline; its role is to check whether the groups were well balanced with respect to the outcome at baseline. The appendix illustrates this deduction more clearly than a reference alone would.

e. “Results: table 1 is redundant as a large proportion of data are not available. The main results are in table 3, which is confusing. It is supposed to present the results of a multilevel model. The numbers (N) presented are actually denominators of a fraction. They should be accompanied with the number of outcomes (numerators). The crude or unadjusted odds ratios should be presented along with adjusted odds ratios. The variable crackle has no meaning as three levels (absent, present and not recorded) do not make any sense.”

Table 1 has been retained because it describes key characteristics of the 1,160 children with non-bloody diarrhoea. It is acknowledged in the discussion that some observations were not recorded by clinicians (this was one of the secondary outcomes of the trial) and that this might introduce some bias in characterising the sample.

We feel that presenting the suggested numbers and crude odds ratios in table 3 is unnecessary as it will result in a cluttered and complicated table, while not adding value or meaning to the main results. Furthermore, if the intention of presenting crude odds ratios in addition to adjusted ones was to satisfy the reader as to the effectiveness of randomisation, this model efficiently does so by showing no evidence of a difference between the groups at baseline. A detailed explanation of this has been included in the appendix that described the model.

f. “In view of the above comments I cannot recommend it for publication in this esteem journal”

It appears to us that this largely negative review arises out of misunderstanding of many elements of this study and the focus of this paper. We disagree with this recommendation because this paper describes an interesting design and methods that to our knowledge are rarely used in clinical research and have not before been used on data from multiple hospitals in low-income settings. We however acknowledge that it may not appeal to readers interested in discussions of statistical methodology alone. We have made an effort to improve it using comments from all reviewers and would like to note that all other reviews were positive; the reviewers made sense of all the issues referred to by this reviewer as unclear or incomprehensible and even recommended very specific improvements. We note that this (statistical reviewer) did not fault the analysis nor its interpretation while other reviewers with a more general view on the paper recognised its value.

Yours sincerely,

Charles Opondo, on behalf of all authors.