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
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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: 9646034375394982

Thank you for your feedback on our manuscript. The following are our responses to these reviewers’ comments:

Reviewer 3:

Authors’ comment: These comments had been raised during the first review. Our response had been as follows: 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:


Reviewer’s second comment: “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? It was asked in my previous comment.”

Authors’ second response: The contents of the training for the two groups are described in the ‘Methods’ section under ‘The intervention’: “The full intervention had several components including: the five-and-a-half day theory and practical training (ETAT+) in recommended practices...” The ‘recommended practices’ referred to in this text are mentioned in the second line of the same paragraph: “Briefly, it involved adaptation of evidence-based practices for assessing, classifying and managing childhood malaria, pneumonia, diarrhoea and dehydration,
malnutrition, anaemia, meningitis, neonatal sepsis and prematurity to the local situation...”

Content of the training for the partial intervention is described in the second paragraph of the same section: “A partial intervention was delivered to ‘control’ hospitals including: the same 1.5 days didactic training on the use of guidelines as in the full 5.5 days course...”

Reviewer’s second comment: “Number of groups the staff (30-34 in full intervention group and 35-40 in partial intervention group) were trained? I could not find answer to this comment.”

Authors’ second response: Numbers of different cadres of staff trained in the two groups are stated in the ‘Methods’ section under ‘The intervention’. In the intervention group: “... 30-34 hospital staff at each intervention site (in total 90 nurses, 11 medical officers and 29 clinical officers providing paediatric care referred to here as ‘clinicians’ were trained across the four hospitals)”. In the control group: “...35-40 hospital staff at each site (107 nurses, 6 medical officers and 21 clinical officers in total across the four sites)”. 

Reviewer’s second comment: “Number of recommended practice discussed during the training in each group? I could not find answer to this comment.”

Authors’ second response: Recommended care practice was discussed for the childhood illnesses listed in the second sentence of ‘The intervention’ section: “Briefly, it involved adaptation of evidence-based practices for assessing, classifying and managing childhood malaria, pneumonia, diarrhoea and dehydration, malnutrition, anaemia, meningitis, neonatal sepsis and prematurity to the local situation with development of management protocols disseminated by the Ministry of Health. Thus, training spanned a large number of recommendations. Recommendations for managing non-bloody diarrhoea alone included appropriate history-taking, assessment for shock and dehydration, classification of severity of dehydration and appropriate rehydration therapy, four key recommendations (of which one was a primary trial outcome - accuracy of intravenous fluid prescriptions).[18] The use of antibiotics for non-bloody diarrhoea was actively discouraged and represented a fifth key recommendation in this area. This management plan was summarised within the clinical protocols provided within guideline booklets for clinicians and nurses and wall charts.”

Reviewer’s second comment: “What were the contents of face-to-face feedback? I could not find answer to this comment.”

Authors’ second response: Face-to-face feedback was an approach to present findings of baseline and 6 monthly surveys during visits by supervisors rather than just in written. This is stated under ‘The intervention’: “Written and face to face feedback focused on key trial outcomes but also provided information on inappropriate antibiotic use for non-bloody diarrhoea amongst many other indicators of quality of care. Face to face feedback was provided by those undertaking supervision six-monthly, however the wider supervisory process (2-3 monthly) was not standardised tending to focus on key, hospital specific problems related to pre-identified key indicators [18] and follow up of locally developed action plans.”

Reviewer’s second comment: “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? It is not clear in the manuscript.”

Authors’ second response: We have further described face to face feedback above and distinguish it from supervision which is now described in the text as: “2-3 monthly supervision of hospitals’ implementation by a paediatrician from the study team to discuss progress in guideline implementation, informed by data from surveys when available (see below), and
identify local strategies for problem-solving with senior hospital staff (described by Nzinga et al.[23]).

Reviewer 4:

a. Background
   i. Reviewer’s first comment: “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)?”

   Authors’ first response: 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.

   Reviewer’s second comment: “Even if a reference to the main study was included, I consider it very helpful to deliver some more details about the main study also in this paper.”

   Authors’ second response: More details about the main study are included in the now extensively revised ‘Methods’ section under ‘The intervention’. These changes are described in detail in our letter of response to reviewers 2, 3 and 5.

b. Methods
   i. Reviewer’s first comment: “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.”

   Authors’ first response: 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.

   Reviewer’s second comment: “Where was this information included into the paper?”

   Authors’ second response: We have now included a sentence in the ‘Methods’ section in the third paragraph of ‘The intervention’ describing the partial intervention and provide a reference to a published report detailing the form of full and partial intervention: “The partial intervention was not typical of this setting; it was better than the support that would routinely have been provided by the Ministry of Health, notably in the provision of written performance feedback.”

   ii. Reviewer’s first comment: “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.”

   Authors’ first response: 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.”

Reviewer’s second comment: “OK. My remark, however, also aimed at the point which endpoints/outcomes were actually predefined in the main study.”

Authors’ second response: We have now described the broad areas from which the main study outcomes are derived in the ‘Background’ (where we state that there were 14 process of care indicators that comprised the main outcomes), the ‘Methods’ and listed the specific outcomes in the ‘Discussion’: “...structure indicators of availability of key resources supporting service delivery, process errors in management of pneumonia, malaria and diarrhoea/dehydration, and outcome indicators of adherence to key policy recommendations).” In addition we now also make the point in describing the intervention that “While the main trial outcomes were thus the focus of intervention it was hoped that by providing a broad set of guidelines, linked to training and an increased emphasis on provision of quality care fostered by the process of supervision and feedback that a wider set of practices might improve.”

iii. Reviewer’s first comment: “The interventions should not only address the use of antibiotics but also rehydration and hygiene aspects. Were those aspects addressed by the intervention?”

Authors’ first comment: 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).

Reviewer’s second comment: “OK. It would be more helpful for the reader to include such important issues (e.g. hygiene) directly in the paper than to refer to related papers.”

Authors’ second response: There is always a balance to be struck in maintaining a paper’s focus and dealing with every interesting issue. We agree that hand-washing is an important issue but our study design did not allow us to assess hand-washing practices. We therefore think it is prudent to limit our discussion to what we can say about a possible link between the intervention and another important practice – appropriate antibiotic use. Thus even though hand-washing with soap and water was promoted as part of an overall approach to promote good
practice the study design was not specifically aimed at assessing this as an outcome and we have no data on adherence to good hand-washing practice. While acknowledging its importance therefore we can make no statement about effect. We do now make this clear with a statement in the paper’s discussion: “While other interventions are also important in reducing the burden of disease and costs attributable to diarrhoea, such as staff hand-washing that was also promoted within the intervention, our study design did not allow us to evaluate any effect of the intervention on these practices.”

iv. Reviewer’s first comment: “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.”

Authors’ first response: 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.

Reviewer’s second comment: “This considerations should be better discussed also in the paper.”

Authors’ second response: We have now stated at the beginning of the ‘Statistical analysis’ section that all children were assumed to have received the group treatment their hospitals had been allocated to and that we undertook analyses that adhere to the intention-to-treat principle.

c. Results

i. Reviewer’s first comment: “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.”

Authors’ first response: 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.

Reviewer’s second comment: “It would have been more helpful to address the comment.”

Authors’ second response: We would be happy to present the figure 2 data in a table if the editors feel this is appropriate, however, the resulting tables would be a large, 29 row-by-3 column table. We feel that such a large table may fail to communicate the relative prevalences of clinical signs as readily as the figure does. We have however improved the contrast and quality of the figure to make it easier to read. As the other reviewers appear to support inclusion of the figure we are thus continuing at present to propose use of the figure – representing the
majority view – but as indicated if the editors feel the table is preferred then we will provide a table.

ii. Reviewer’s first comment: “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.”

Authors’ first response: 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 uncertainly, 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.

Reviewer’s second comment: “I am not sure whether this remark is sufficiently addressed also in the paper/discussion.”

Authors’ second response: This issue has been addressed in the discussion; to be specific, we have described how we factored in various sources of variation in estimating the intervention effect: “...between-clinician differences contributed almost two-thirds of overall variability in the data...” We have sought stronger evidence of an intervention effect by examining intervention-time interaction (a form of dose-dependency of the intervention effect): “A new finding was some evidence that the intervention effectiveness was modified by survey period; this suggests a dose-dependent effect on the outcome. Thus the accelerated improvement in the intervention arm compared with the control arm suggests a true effect of the full intervention.” The average clinical impact of the intervention was estimated to be substantial – an odds ratio of 0.30 for the association of intervention with inappropriate antibiotic prescribing. In the paper we describe this potentially very important clinical effect in the discussion but we feel, appropriately cautious given the borderline statistical significance (that is partly because of heterogeneity across hospitals): “Both procedures provide comparable weak evidence of a possibly substantial intervention effect, with the individual level model indicating that children in the intervention hospitals had just under one-third the odds of receiving antibiotics inappropriately compared to those in the control hospitals by the trial endpoint.” We also feel it is worth noting that most studies of guideline adherence are based in one hospital site – the fact that we observe an intervention effect despite variation across hospitals actually makes our findings much more generalisable than studies reporting from one place.

d. Discussion
i. Reviewer’s first comment: “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.

Authors’ first response: 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.

Reviewer’s first comment: “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).”

Authors’ first response: 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.

Reviewer’s second comment: “Where have those aspects been included into the paper?”

Authors’ second response: We have now stated in the discussion that most studies we have reviewed “...have been poor quality individually randomised studies or studies in primary healthcare settings that are not comparable to hospitals in a low income country...” and further we have designed our statistical analyses “... in acknowledgement of the reality that the hospital is the unit of intervention...” Additionally (in relation to the reviewer’s first comment about the discussion) perhaps the editors would consider inviting a commentary piece on our manuscript that can deal with the wider issues of guidelines adherence.
ii. Reviewer’s first comment: “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).”

Authors’ first response: 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.

Reviewer’s second comment: “I believe that this answer did not address my remark appropriately, e.g. considering a comparison of so called developed and non-developed countries.”

Authors’ second response: In the discussion we have stated that such comparisons are difficult because in the literature we have reviewed the study designs and populations are not similar to our study: “However most of these studies have been poor quality individually randomised studies or studies in primary healthcare settings that are not comparable to hospitals in a low income country” In addition we address this point in the final part of the paper: “We are not aware of any other studies evaluating an intervention intending to improve care for multiple, common and life-threatening illnesses in children admitted to hospitals in low-income settings using a randomised controlled design. The intervention provided training on evidence-based paediatric care with facilitation, supervision and feedback delivered at the hospital level. In the analyses presented we show that the intervention substantially reduced the odds of a child being inappropriately treated with antibiotics for non-bloody diarrhoea, an improvement in care that is in addition to the findings of improvement in most of the 14 process of care indicators forming the primary endpoint for the trial [18]. Most previous intervention studies to improve care, in both developed and developing countries, have focused on single diseases and have often demonstrated only modest improvements in practices. The data we bow report indicates even wider benefits of the intervention than suggested in the main study results implying that the intervention effects may cut across all diseases covered by the guideline package approach. Other ongoing analyses of the intervention suggest that it requires modest financial investments for comparatively substantial improvements in quality of care. Enhanced medical education focusing on rational use of antibiotics is necessary to improve clinicians’ prescribing habits; we have shown that it is possible to change practices using an integrated approach and that perhaps, at hospital level, this is preferable to the recent focus on disease-specific interventions within low-income settings.”

iii. Reviewer’s first comment: “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.)?”

Authors’ first response: 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.

Reviewer’s second comment: “Once more, the word limitation cannot be used as an apology. There are a lot of statistical aspects that should be considered to chose the appropriate methods, however, they are not so important for clinical consideration. I believe that those interesting aspects should be included into the paper.”

Authors’ second response: Going back to the reviewer’s initial question: the ‘false treated patients’ referred to are not the subject of this analysis and are excluded from the sample under consideration. Furthermore it is not possible in Kenyan hospitals (nor in most low-income settings) to test for the causative organism of diarrhoea and such data are thus not available to inform further analyses of the trial data. It would seem inappropriate to speculate in the discussion on the potential importance of this issue without such data. Once again perhaps the editors would like to invite a commentary on our paper that considers these much wider issues and can draw on what literature are available on aetiology of inpatient diarrhoea in children in low-income settings and the actual risks of inappropriate antibiotic therapy. We feel the reader already has much to think about when reading our report and would rather maintain some kind of focus on whether the intervention had an effect and a discussion of appropriate methods to examine such an effect.

We hope that this revision now fully addresses the reviewer’s comments.

Yours sincerely,

Charles Opondo, on behalf of all authors.