Reviewer's report

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

Version: 3 Date: 20 October 2011

Reviewer: Thilo T Bertsche

Reviewer's report:

some further "Discretionary Revisions" mentioned below should be considered by the authors

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.

=> OK

ii. “I wonder if ‘endpont’ 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.

=> OK

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.

=> OK

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.

=> 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.

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.

=> Where was this information included into the paper?

ii. “The authors should provide some information about the economic impact of the interventions. The strategies in the intervention groups seem to be rather costintensive 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.

=> OK

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.”

=> OK. My remark, however, also aimed at the point which endpoints/outcomes were actually predefined in the main study.

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.”

=> OK

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.

=> OK

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).

=> 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.

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.

=> This considerations should be better discussed also in the paper.

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.

=> It would have been more helpful to address the comment.

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.

=> I am not sure whether this remark is sufficiently addressed also in the
paper/discussion.

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.

=> I still feel that clinical aspects should be better addressed (e.g.
some considerations of the figures as mentioned also above). The limitations of
words cannot be used as an apology in my opinion.

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
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.

=> Where have those aspects been included into the paper?

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.

=> I believe that this answer did not address my remark appropriately, e.g. considering a comparison of so called developed and non-developed countries.

“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.

=> 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 included into the paper.

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.

=> OK