Author's response to reviews

Title: Appropriate Antibiotic Use for Patients with Complicated Urinary Tract Infections in 38 Dutch Hospital Departments: a Retrospective Study of Variation and Determinants

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Version: 3
Date: 27 September 2015

Author's response to reviews: see over
Amsterdam, September 26th 2015

Re: MS 1261297231695855

Dear Dr Iruka Okeke,

Thank you for your email dated July 30th concerning the manuscript "Appropriate Antibiotic Use for Patients with Complicated Urinary Tract Infections in 38 Dutch Hospital Departments: a Retrospective Study of Variation and Determinants”. We appreciate your decision to consider a revised manuscript for publication in BMC Infectious Diseases.

We have carefully reviewed the comments raised by the academic editor and the reviewers. Below, please find our responses to their comments.

Thank you very much for considering this manuscript for publication in BMC Infectious Diseases. We are looking forward to receiving the Journal’s review of the revised manuscript.

Yours sincerely, on behalf of all authors,

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REVIEWERS’ COMMENTS

Reviewer 1:

Major Compulsory Revisions
General comments:
The manuscript describes an important public health issue in the Netherlands regarding appropriate antibiotic use in patients with complicated urinary tract infections. The study was carried out in a relatively large study population (1,964 patients) with a complicated urinary tract infection treated at Internal Medicine and Urology departments of 19 Dutch hospitals, and it was based on the accurate diagnosis by treating physicians. The dependent variables used in this study were the QIs applicable in the Dutch health system. The independent variables covered both demand sides and supply sides. However, I have several concerns with the way that the paper has been written, in particular with its overwhelming information and remarkable variations of the findings.

We thank the reviewer for his comments on the relevance of the manuscript. Below, please find our responses to the comments.

1. Is the question posed by the authors well defined?
Yes. But the scope of question is huge, which might be difficult to answer as a whole.

2. Are the methods appropriate and well described?
The study setting, data collection, analytic variables and indicators were well described. But there were too many aspects and dimensions, including type of departments, kind of UTI (febrile or non-febrile), demographical and clinical characteristics of patient, a group of stewardship elements, and 9 QIs.
Although multivariate analysis was applied, the large variation in QI performance between departments, type of patients, QIs, and the variables having a significant OR suggests the uncertainty of findings, and the impacts of findings might also been diluted due to put everything together. Stratification should be taken into consideration. My suggestion is targeting patients who are under the most concerns regarding antibiotic treatment, and stratifying them into comparing groups according to the research questions such as febrile and non-febrile, teaching hospital or non-; department A or B,C, inpatient or outpatient, etc. Also I don’t think the stewardship elements should be included in this paper. With so many dimensions and aspects, the contribution of each element is hardly counted. Let alone, quite a few of these elements has the potential for collinearity.

The study design was explorative in nature, looking at potential determinants for a good QI. We agree with the reviewer that we included many determinants of antibiotic use, also including stewardship elements. This is in line with the current insight that various determinants, at various levels (i.e. patient, department and hospital), might influence the appropriate prescription of antibiotics and cause antibiotic use to vary in different hospitals [1]. In previous research, many of these single determinants turned out to be factors that influence antibiotic use [1]. Therefore, an important aim of our study was to evaluate these various determinants in one (explorative) model to identify determinants at which future improvement interventions should be focused. With the implementation of antibiotic stewardship programs at a large scale throughout the world, adding different stewardship elements to our analysis was crucial.
The reviewer is right that there is a risk of collinearity. However, we calculated the correlation coefficient of each pair of determinants. If two independent variables were highly correlated (correlation coefficient >0.6), only one variable was included in the analysis (see Additional File 1). We also evaluated the consequences of using more rigorous cutoff points (correlation coefficient between two determinants >0.4) or less rigorous cut-off points (coefficient >0.8) (see Methods section, lines 181-185, also Results section, lines 270-272).

It is true that a large variation was demonstrated between departments in performance scores of the QIs. Regarding to this, in our multivariate analysis, we modelled the variation over departments as random effects (not fixed). We do not agree with the reviewer to perform stratified analyses. A stratified analysis is the same as an overall analysis that includes interaction terms between the strata and all other covariates. In general, it will result in loss of power because an unstratified analysis can leave out interaction terms. Note that, since our study design was explorative, only associations can be demonstrated. Causal relationships cannot be inferred (see Discussion section, lines 374-375).

3. Are the data sound?
Yes. Although there are missing data, data collection is well organized.

4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
   - To present the most meaningful and important results, the performance of each QI should be described in details, instead of being graphed together in Figure 1. What the readers/users would like to know is: what kind of patients had the lowest QIs, and which QI was at the lowest?

As asked by the reviewer, we added in the text which QI was at the lowest and which QI was at the highest (see Results section, lines 225-226). In addition, to present the performance of each QI, we think that the figure (1) is very informative and suitable, displaying box-percentiles plots, including all individual department scores, as well as the median, 30th and 70th percentiles. Describing all these details in text, is difficult and would take many words.

To answer the question what kind of patients had the lowest QIs, readers are referred to the descriptions in the Results section, to table 2 (determinants of QI scores) and to Additional File 2 (new, see next point of the reviewer). So, for example, patients at risk for receiving empirical therapy not according to the local hospital guideline were patients with a urinary catheter, patients who received antibiotic therapy prior to admission and patients with a non-febrile UTI (see Results section, lines 242-244).

   - For each QI, it is better to report the results (OR, CI%) of all variables in the multivariate analysis, rather than only report the results for variables with statistical significance.

We followed the suggestion of the reviewer and added a table (see Additional File 2) with the results of all variables in the multivariate analysis, rather than only the variables with statistical significance. Because of the size of the table, we thought creating an additional file would be preferable.

   - Tables should be presented in the 3-line format

As stated in the Instructions for Authors, columns and rows of data (in tables at the end of the manuscript) were made visibly distinct by ensuring that the borders of each cell display as black lines.

5. Are the discussion and conclusions well balanced and adequately supported by the data?
Discussion and conclusions are well balanced but due to the abundant information it is difficult to see the impacts of findings.

6. Are limitations of the work clearly stated?
Limitations of the work are partly clearly stated.

7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished?
I think so.

8. Do the title and abstract accurately convey what has been found?
Yes.

9. Is the writing acceptable?
The writing is acceptable. The results should be presented consistently in the past tense. We checked that the results were presented consistently in the past tense.

Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Needs some language corrections before being published
Statistical review: Yes, and I have assessed the statistics in my report.

Reference

Reviewer 2:

This is a well written manuscript reporting an interesting study. Some comments noted below

We thank the reviewer for her comments on the manuscript. Below, please find our responses.

Major Compulsory Revisions
The abstract is not giving full justification to the paper. Please make it more clear. Examples are that sex of included patients may be mentioned and the sentence 'In particular patient characteristics were associated with less appropriate antibiotic treatment.' What is meant? These two are examples, please revise the abstract in detail.

As suggested by the reviewer we revised the abstract and provided some clarifications (see **Abstract**).

Please be consistent throughout the manuscript with the terminology. In the beginning 'Antimicrobial' (Always this confusion antibiotic/antimicrobial, better to be specific if not antivirals, antifungals and antiprotozoal drugs are included) is often used while I think what is refereed to is 'antibiotic'. Also towards the end the term used is 'antibiotic'.

We agree with the reviewer and specified the term ‘antimicrobial’ at several places in the manuscript as ‘antibiotic’ (line 78, 79, 81, 130, 299, 308). In this manner, terminology is consistent throughout the manuscript.
In the definition it is said 'We defined a complicated UTI as a UTI with one of the following characteristics: male gender, pregnancy, any functional or anatomical abnormality of the urinary tract, immunocompromising disease or medication, or a UTI with symptoms of tissue invasion or systemic infection'. Should it be 'one or more' or was it always only one?
It should be ‘one or more’. We changed this in the manuscript (see Methods section line 107-108)

The data from records were collected in 2009 (for the year before), the questionnaire done in 2010 and now it is 2015, please explain the delay. Also please explain what was asked in 2010, the present situation at that point or the situation during the study period.

We understand the question of the reviewer about the time delay between data collection and manuscript submission (5 years). The reason for this a pragmatic one. As pointed out in the Methods section (line 100-102) the actual study presents the baseline results of a cluster randomized controlled trial testing a multifaceted stewardship program to improve the appropriateness of antibiotic use in UTI patients. So after baseline data collection (as presented in the actual manuscript) the study researcher was occupied with an extensive implementation program in 9 hospitals/18 departments, as well as post-intervention data collection in 19 hospitals/38 departments.
In the questionnaires filled in by an internal medicine physician and an urologist we asked about the actual situation at that point, except from asking about quality improvement projects concerning antibiotic prescribing and changes in antibiotic procedures in the past 3 years.

Line 251-254 it is said 'Tailor antibiotic treatment on the basis of culture results’. At departments where internal medicine physicians or urologists received feedback about pathogen-directed therapy after determination of the blood or urine culture results, patients received less culture-guided, tailored therapy.' This is quite difficult to understand. It is slightly addressed in the discussion but a more indepth discussion about this would be warranted.

The inverse relationship between receiving feedback about pathogen-directed therapy and tailoring antibiotic treatment is indeed difficult to understand. In literature we could not find useful theories, so in our discussion we could only speculate about the explanations for this paradox and that’s why we are careful with it. As we mention in the discussion, an explanation could be that our question was about feedback on culture results in general, not specifically for feedback on UTIs. In addition, we defined feedback as ‘incidentally or structurally individual advice’; we made no distinction between the two forms.
Hypothetically, if feedback on blood cultures was structurally provided, but feedback on urine cultures was not (or incidentally), it may have an inverse effect on tailoring therapy for UTIs. We extended this explanation in the discussion (see Discussion section, lines 338-340).

Further in line 257 'Treatment duration was less appropriate in female patients: in general their treatment durations were shorter than recommended in the national and local hospital guidelines' It would be good if the content of the national and some local guidelines would be mentioned somewhere. As stated in discussion the movement is now towards shorter treatment duration.
As asked by the reviewer we added the treatment duration as recommended in the national and local hospital guidelines in the manuscript (see Results section, line 260).

Line 264 'However, quality improvement projects in the past three years concerning antibiotic prescribing were inversely associated with this QI. This negative association was also shown
for the QI ‘Treat every man in accordance with the local guideline’. Also this would need some interpretation.

The association between quality improvement projects in the past three years and less appropriate treatment of UTI in men is another example of a paradox. In line with the previous one, it is important to realize that we asked for projects concerning antibiotic prescribing, not specifically for UTIs or UTIs in men, so unintended effects (concerning this QI) might have played a role. We extended this explanation in the discussion (see Discussion section, lines 340-344).

Line 313, difficult to understand, isn't it so that males more or less by definition is considered complicated when it comes to UTI?
The reviewer is correct; every UTI in men should be considered as a complicated UTI. However, in practice, it seems that febrile UTIs in men are more easily recognized as complicated UTIs than the non-febrile ones.

So discussion including also methodological considerations need to be modified.

Minor Essential Revisions
Please read carefully and correct any small mistake found.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report

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Editorial requests:

- Please confirm whether informed consent from all patients was obtained or whether the need for informed consent was also waived by an IRB.

The Ethical Committee of the Academic Medical Centre Amsterdam considered our study and concluded that our study was deemed exempt from their approval (ref 08.17.1775). No informed consent was obtained from patients because no interventions at the patient level were done (implementations were done at the department or hospital level) and patient data were analyzed in a retrospective design anonymously for the aim to improve quality or healthcare. Informed consent was obtained from the contact persons of the participating hospitals. We added this explanation to the manuscript (**See Methods section, lines 119-122**).

- Please remove the section Funding and detail funding in the Acknowledgements section We did.

-Please provide a section containing information on additional file 1 at the end of the manuscript, as detailed in the Instructions for Authors:
  
  [http://www.biomedcentral.com/bmcinfectdis/authors/instructions/researcharticle#preparing-additional-files](http://www.biomedcentral.com/bmcinfectdis/authors/instructions/researcharticle#preparing-additional-files)

  We did.