Author’s response to reviews

Title: Trends in antimicrobial management of gonorrhoea by general practitioners in Amsterdam, the Netherlands, between 2010 and 2016: A cross-sectional study

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Version: 1 Date: 10 Oct 2018

Author’s response to reviews:

Dear editorial board,

Thank you very much for the review of our manuscript entitled: ‘Trends in antimicrobial management of gonorrhoea by general practitioners in Amsterdam, the Netherlands, between 2010 and 2015’.

We are grateful for the constructive comments and suggestions of the reviewers, and we include a point-by-point reply. One of the revised versions of the manuscript contains track changes to indicate all changes, the other version contains revisions without mark.

We hope that the current version of the manuscript has become suitable for publication in BMC Family Practice.

Sincerely yours,

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In Reply to Reviewer: 1
Reviewer 1 (Joseph Lee) Comments for the Author.

Overall this was an interesting read, the methodology seems appropriate and the conclusions relevant and I have recommended it for publication. I have a few suggestions that I think would strengthen the paper and there are quite a few minor changes that could clarify the English.

We are very grateful to the reviewer for the positive comments and suggestions.

1) Incidence of gonorrhoea - I wonder if confidence intervals would add something? e.g. Figure 2.

We agree with the reviewer and we added the confidence intervals in Additional Table 2.

2) Trends - this is mentioned in the title so I was expecting a statistical assessment of trends. e.g. Antimicrobial Management - line 147 states infections treated with the correct antibiotics increased significantly, is this statistical significance? if so how was this calculated.

The reviewer has a valid comment. Statistical analysis has been carried out to demonstrate the trend of ceftriaxone prescriptions in the period 2010 to 2016. We added Additional Table 3 to show how the percentage of guideline adherence per year has been calculated.

I may be misinterpreting fig 3 as I have it in greyscale but it looks to me that the 2010 figure for cefotaxime plus ceftriaxone is about 81% and 2016 94%? (as opposed to 77% and 97% in the text) Could you check this?

We thank the reviewer for his comment. We clarified figure 3 and corrected the percentages of cefotaxime plus ceftriaxone in the manuscript.

3) Antibiotic treatment preferences: line 161 onwards, I prefer the use of 15/34 to percentage when the number is low, though this is arguably a personal preference and I note you have provided both.

In our case we provided both.

4) For the international readership - is there anything beyond the described demographics that might be different/special about this part of Amsterdam? (There may not be, but I can imagine that as in many large cities there might be e.g. socioeconomic differences between areas)

We thank the reviewer for this observation and added details about the socioeconomic status and ethnic background in Methods (setting).
5) English: Whilst the English is of a high standard and completely understandable there are opportunities to polish it should the editors prefer to do so. Here is a list of suggestions. Sorry for being picky, these are offered in the spirit of trying to be helpful. :-) 

Line 23: The Dutch guideline has recommended a single dose of.... 
We clarified the sentence.

Line 29: years 2010 to 2015 
The error is corrected.

49: So far few cases of ceftriaxone-resistant gonococcal strains have been identified 
We changed the sentence.

52: delete 'one of the last blind' 
This has been deleted.

55: ...the major part of STI care is provided by GPs 
61: delete 'in particular' 
This has been deleted.

62: demonstrated that the majority of GPs 
We changed the sentence.

95: in patients aged 15 years and older who received.... 
We changed the sentence.

99: (a positive test in a sex partner) 
We changed the sentence.
106: ...obtained on the opinion of...
We changed the sentence.

110: ...agreement with each statement...
We changed the sentence.

116: Can you clarify '(annual report GAZO)'
We clarified the sentence.

112: ...alternative antibiotic therapies... (I think this is important to clarify as 'alternative therapies' implies non-standard care e.g. homeopathy)
We clarified the sentence.

161: you could delete 'a total of' then say: 34 GPs were eligible for the survey to assess experiences...
This has been deleted.

185: Only 64% of GPs in 2010 administered antibiotics recommended for the treatment of gonorrhoea.
We changed the sentence.

214: ...sample size in a highly urban area with a high prevalence...
We changed the sentence.

216: not representative of the Netherlands.
We changed the sentence.

218: ...coding errors which may have...
The error is corrected.
222: high prevalence area...

We changed the sentence.

Fig 4: IM administration of cephalosporin (not Im)

We changed the sentence.

Fig 4: Preference for single dose...

We changed the sentence.

Fig 4: Preference for culture-based...

We changed the sentence.

In Reply to Reviewer: 2

Reviewer 2 (SC Chen) Comments for the Author.

We thank the reviewer for the positive and constructive comments.

1) The 2016 WHO STI guideline suggests dual therapy (one of the following: ceftriaxone plus azithromycin, or cefixime plus azithromycin) over single therapy (ceftriaxone when the recent local resistance data confirming susceptibility to the antimicrobial) for people with gonococcal infections. Please revise the relevant description in the background section.

We thank the reviewer for this observation and revised the description in the background section based on several international guidelines and recommendations of most European countries (instead of only the recommendations of the WHO). In the Netherlands dual therapy with azithromycin is only advised if a Chlamydia trachomatis coinfection is suspected or diagnosed. Since it is uncertain whether dual therapy has additional benefit in the control of antimicrobial resistance compared with monotherapy (as gonorrhoea infections can be cured by a single-dose antibiotic), in the Netherlands monotherapy has been recommended (Xiridou et al. 2016). Furthermore, recent studies even hypothesize that exposure to azithromycin may induce resistance (Wind et al 2017. Clin Infect Dis, Horner et al 2016. Sex Transm Infect.).

2) In the background section, please provide the relevant reference(s) regarding the description of "A previous report demonstrated that a period of five years was needed to implement an update in the Dutch STI-guideline—a change in preferred medication for gonorrhoea to an
intramuscular third-generation cephalosporin- in just 64% of general practitioners (GPs) between 2005 and 2010".

We provided the reference.

3) In the background section, please provide the relevant reference(s) regarding the description of "Since 2013, the updated Dutch guideline recommends a single intramuscular dose of ceftriaxone for the treatment of gonorrhoea".

We thank the reviewer for his comment and changed this accordingly.

4) The descriptions of "Data on STI-related episodes and STI-diagnoses for gonorrhoea…from 35 GPs for the year 2010 until 2015" in abstract and "From 2010 until 2015, 263 cases…" in the results section were not in concordance with the descriptions regarding the study period ("a 6-year period from January 1st 2010 to January 1st 2016” on page 4, and "the period from 2010 to 2016” on page 9) in the methods and discussion sections. Please revise them.

We changed this throughout the manuscript in order to report consistent time frames.

5) How to design the online questionnaire regarding GPs' experiences with the administration of intramuscular third-generation cephalosporins? Please provide the data regarding the validity and reliability of this questionnaire. Why did the study get the data of the questionnaire without approval from an institutional review board? Please clarify them.

We thank the reviewer for his comment. The three exploratory questions have been composed to gain insight in GPs experiences with the recommended intramuscular administration of third generation cephalosporins. No validated questionnaires were needed to get this impression. Data of the questionnaire could be obtained without approval from an institutional review board because the database contains anonymized electronic health records. GPs participating in this research network (General Practice Department research database of the Amsterdam University Medical Center (AUMC), location southeast) are aware of data usage.

6) Please provide the data regarding the treatment failure rates of dual therapy vs. single therapy (or the treatment following the guidelines vs. the treatment not following the guidelines,…, etc.). The information would be interesting to readers.

We agree with the reviewer and added Additional table 3 to provide the data regarding guideline adherence vs. non-adherence. Data regarding the treatment failures was not reported.

In Reply to Reviewer: 3
Reviewer 3 (Lisa M McCarthy) Comments for the Author.

General Comments:

This cross-sectional study reports the 5-year patterns toward guideline concordance in gonorrhoea treatment with first-line intramuscular ceftriaxone between 2010 and 2015 in Amsterdam, The Netherlands. This manuscript would be strengthened by the addition of more context regarding the rationale for the 2013 Dutch Guidelines update (i.e., susceptibility data that supported the removal of cefotaxime as a first-line treatment option) and by including details regarding the development and administration of the survey in the Methods. Other opportunities to improve the manuscript include clarifying the consistency of the reported Results between the text and figures and discussing additional limitations.

We are very pleased with the positive comments and the suggestion for several amendments on the text. First, we added more text regarding the rationale for the Dutch guideline update in the background section.

Title:

1) Please add the study design to the title per the submission guidelines. (i.e., Trends in antimicrobial management of gonorrhoea by general practitioners in Amsterdam, the Netherlands, between 2010 and 2015: A Cross-sectional study).

We changed this accordingly.

Abstract:

1) Throughout the manuscript, both 2013 and 2014 are cited as the year of the guideline update. (e.g. 2013 in lines 23 and 64 and 2014 in lines 119 and 150). Please reconcile.

The reviewer is correct, we are aware that we used both years. The updated guideline was published end of 2013, so we defined 2014 in our study as mark off for the two periods in which a specific guideline was recommended. In the period 2010 to 2014 we accepted both cefotaxime and ceftriaxone as first choice treatment, from 2014 onwards only ceftriaxone was defined as recommended therapy.

2) The Results provided in the abstract may not accurately capture the article's content. The overall aim is to "investigate trends in the antimicrobial management for the treatment of gonorrhoea". It is unclear however, whether the aim was to investigate prescribing concordance with the 2013 guideline update or if it was to simply convey the change in the rate of ceftriaxone prescribing. It is presumed by the reader that the authors intended to demonstrate guideline
concordance as the data analysis method chosen was "the annual percentage of administered first choice treatment according to the guidelines was reported" (lines 116-117). From this data the authors conclude that "The results demonstrate a successful shift in the antimicrobial management of gonorrhoea infections to ceftriaxone monotherapy according to the national guideline." (lines 38-39). For this reason, reporting the change in the rate of ceftriaxone monotherapy between 2010 and 2015 is potentially misleading as cefotaxime was also an equally appropriate, recommended option from 2010 to 2013. It may be more appropriate to report the difference in the rate of ceftriaxone monotherapy prescribing between 2013 and 2015.

We agree with the reviewer that this might be confusing. This description has been revised by documenting the rate of infections treated with first choice therapy over the years (cefotaxime or ceftriaxone until 2014 and only ceftriaxone since 2014). But we also kept in the difference in the rate of ceftriaxone prescriptions because this concurs with the hypothesis about the implementation of the current guideline.

3) The results and conclusions from the survey require support from an expanded discussion on the methods used to create and administer the questionnaire. Please see Methods below.

Background:

1) Dividing the first paragraph into smaller sections would help the readability of this section. Suggested natural breaks would be in line 55 before "In the Netherlands…", line 59 before "It has recently been shown in Estonia…", and line 63 before "Since 2013…".

We thank the reviewer for the suggestion and divided the paragraph into smaller sections.

2) The manuscript would be greatly enhanced by expansion on two particular concepts introduced in this section.

   i. Impetus for this study: Lines 56-59 briefly mention a previous report that appears to be the inciting factor for this investigation. Lines 185-189 address this, but it is unclear why this is relevant. Since the reference is not available in English, the reader would greatly benefit from understanding who the "64% of general practitioners" represent since it is understood that these GPs are not the same as the group included in the present study.

   We clarified the representation of this research population in the background section (A previous report….2005 and 2010.) Furthermore we added lines 70-77 (So far, implementation…intramuscular cephalosporins) to address the aim of the study.

   ii. The Dutch Guidelines: The comment regarding the guideline update in lines 64-65 does not provide the reader with enough context for the rationale of
recommending only ceftriaxone monotherapy. Please provide a reference to these guidelines and clarify: (1) which author(s)/organization wrote and published the guidelines (if available, could also speak to the methods used to develop the guidelines e.g., was GRADE used? http://www.gradeworkinggroup.org/), (2) which third generation cephalosporins are available in the Netherlands, (3) why cefotaxime was taken out of the guidelines, and (4) what susceptibility patterns were used to narrow the WHO guidelines?

(1) The reference has been added and include the names of the authors. (2&3) Third generation cephalosporins available in the Netherlands are cefotaxime, ceftazidime and ceftriaxone. Since 2013 ceftriaxone has been the recommended therapy in gonorrhoea infections instead of cefotaxime because of a more favourable pharmacokinetic profile. (4) In the Netherlands dual therapy with azithromycin is only advised if a Chlamydia trachomatis coinfection is suspected or diagnosed. Since it is uncertain whether dual therapy has additional benefit in the control of antimicrobial resistance compared with monotherapy (as gonorrhoea infections can be cured by a single-dose antibiotic), in the Netherlands monotherapy has been recommended (Xiridou et al. 2016 Sex Transm Dis). Furthermore, recent studies even hypothesize that exposure to azithromycin may induce resistance (Wind et al 2017. Clin Infect Dis, Horner et al 2016. Sex Transm Infect.).

3) Suggest removing lines 60-63 regarding international rates.

We appreciate the comment, but we think these international rates demonstrate that vast guideline implementation is difficult while it is an important factor to delay further resistance development in times of threatening multidrug resistant gonorrhoea.

4) The last sentence describing objectives of the study should be revisited to ensure that each aim can be matched to a method and a result. For the reader to interpret the results of the investigation of preferences and potential barriers, more context needs to be provided in the methods regarding the survey. Please see Methods below.

We agree with the reviewer and clarified the objectives of the study in the abstract and background section. In methods, we emphasized that we used a cross-sectional study to investigate the guideline implementation and a survey to gain insight in GPs experiences with the recommended therapy.

Methods:

1) Suggested enhancements under each subheading include:

   a. Design:

   i) Please specify what type of gonorrhoea cases were analyzed. (i.e., were oropharyngeal, anorectal, or treatment-resistant cases of gonorrhoea included?)
We thank the reviewer for this observation and added the type of gonorrhoea cases that were analysed to the design.

b. Setting:

i) Please clarify whether gender or sex (or both) are available in the database. Physiological sex is recorded in most databases as opposed to gender.

The reviewer is correct. We changed the error (gender to sex).

ii) Lines 82-84 regarding ethics would ideally be presented at the end of the Methods section.

We agree with the reviewer and moved the lines regarding ethics to the end of the Methods.

c. Data Collection:

i) Please clarify what data was collected from the research database in addition to the ICPC-1 code (i.e., sex, date of birth, antibiotic, diagnostic rationale, etc.).

Details regarding the data that were collected from the database have been clarified.

ii) Please discuss how the 6-year period from 2010 to 2016 was chosen. Was this to present data 3 years before and 3 years following release of the guideline?

To gain insight to the guideline implementation we wanted to include a period of at least two or three years before publication of the guideline. A previous study, mentioned in the background section, investigated the national trends in antimicrobial management in the treatment of gonorrhoea by GPs until 2011. Our study could be a follow up to this previous study. In the General Practice Department research database of the Academic Medical Center data until 2016 was available.

iii) The reader requires more context regarding the choice of ICPC-1 codes to use in case identification. Please discuss how additional related conditions were excluded (e.g. cervicitis, pharyngitis, etc.). Please also address how the cases identified as urethritis or epididymitis were determined appropriate for inclusion if the gonorrhoea code was not used.

We added more context regarding the choice of the included ICPC-codes.

iv) Please specify in line 97 if the treatment indications are derived from the WHO guidelines or the Dutch guidelines.

We added the reference of the Dutch guideline.

d. Suggest adding a subheading called 'Survey Design' between Data Collection and Data
Analysis:

We thank the reviewer for the suggestion and added a subheading called ‘Survey Design’.

i) The paragraph in lines 103-110 could be contained under its own subheading as greater detail is required regarding the development and administration of the questionnaire. This section would ideally address the following questions:

1. Who designed the questions?/How was consensus obtained?

2. How were statements actually phrased on the questionnaire? (Taking into account possible non-direct translations, of course.)

3. How many times were the GPs reminded to complete the questionnaire?

We agree with the reviewer and added details regarding the questionnaire to the new subheading ‘Survey Design’.

e. Data Analysis:

i) Please clarify what is meant by "characteristics of diagnosed gonorrhoea".

We clarified the characteristics in data collection already.

ii) Annual report GAZO in line 116 requires a reference if publically available.

We thank the reviewer for the observation. We described GAZO instead of mentioning the term and added the reference: The incidence was calculated based on the yearly registered patients in the participating health centers in southeast-Amsterdam.

iii) Consider removing lines 122-124 as they are not necessary in this section.

Lines 122-124 were removed.

Results:

1) It would be beneficial to add a statement about the excluded cases being outlined in Figure 1 to direct the reader to the graphic for these details.

We extended this part by adding a statement about the excluded cases being outlined in Figure 1 (From 2010 … settings).
2) This section would greatly be strengthened by clarification of the term "microbiologically confirmed" as this term is not used in the WHO Guidelines. It is presumed the authors intend for this term to encompass culture, NAAT, and gram-stain confirmed cases.

   a. Line 140 states that 36% (98/276) of cases were confirmed via culture. Please include the proportion of cases confirmed via NAAT and gram-stain.

The reviewer is correct that we intended to encompass culture, NAAT or gram-stain confirmed cases so we clarified this term in the manuscript.

   b. In line 139, n=24 whereas in Figure 1, partner management (n=16) and syndrome management (n=18) add up to n=34. Please reconcile.

We thank the reviewer and corrected the number in the manuscript.

3) In line 147, the rate of cefotaxime and ceftriaxone prescribing in 2010 is given as 77% whereas it appears closer to 81% in Figure 3. Please reconcile.

We thank the reviewer for his comment. We clarified figure 3 and corrected the percentages of cefotaxime plus ceftriaxone in the manuscript.

4) The results provided under 'Antibiotic treatment preferences' are difficult to interpret without knowing how the statements were actually phrased on the questionnaire. It may be more reader-friendly to provide the results in a table, as opposed to the graph in Figure 4. The graph is incomplete since it is does not acknowledge that two bars are missing ('strongly agree' in question 1 and 'strongly disagree' in question 2). When grouping responses on a Likert scale, it is optimal to specify what categories are being combined (e.g. to rephrase lines 163-164, "Sixty per cent (n=9) of GPs disagreed or strongly disagreed that intramuscular administration of ceftriaxone is experienced as a cumbersome procedure").

We agree with the reviewer and changed Figure 4. Furthermore we specified what categories are being combined in the text. The exact translations of the statements were documented in the Figure, so that is how they were phrased on the questionnaire.

Discussion:

1) For consistency, suggest specifying the dates in line 177 (e.g. from January 1, 2010 to January 1, 2016).

This has been changed throughout the manuscript.
2) Again, providing more details in the methods may validate the conclusions drawn from the responses. As of right now however, it appears inaccurate to say that "GPs did not experience barriers" (lines 40, 180, 210). Since the questions were posed on a Likert scale, the respondents presumably did not have an opportunity to provide their perceptions of perceived barriers in an open-ended question and thus, there is no way to definitively rule out that the GPs did not perceive any barriers.

We agree with the reviewer. The questionnaire has been used to get an impression of the experiences of GPs with the recommended therapy. To draw more reliable and representative conclusions a more validated survey including open-ended questions should have been carried out. We added this notification to limitations.

3) The rationale for comparing the results of the referenced study [8] to the results of this investigation does not translate particularly well for the reader, as stated in Background above. Report [8] appears to have assessed the proportion of practitioners adhering to guidelines while this study examined the proportion of cases treated per guidelines.

We corrected this in the background section and discussion as the referenced study also investigated the proportion of gonorrhoea infections treated with a specific antibiotic.

4) Please support the statement in lines 186-189 with a reference. Who is expecting the GPs in the AMC to be earlier adopters of guidelines?

The assumption that GPs participating in the network of the AUMC will be earlier adopters of guidelines is based on expert opinions.

5) It is unclear why the comparison to other jurisdictions is particularly relevant in this manuscript as the objective was to characterize the trends in gonorrhoea management in GPs offices in Amsterdam. Some of the discourse is contradictory to the conclusions of this study and the overall message is unclear.

We thank the reviewer for this comment, but we think these international rates demonstrate that vast guideline implementation is difficult while it is an important factor to delay further resistance development in times of threatening multidrug resistant gonorrhoea.

Limitations:

1) Please consider including a statement about limitations associated with the survey (e.g. response rate of less than 50%, non-direct translations of the questionnaire statements, etc.).

We included limitations associated with the survey.
Conclusions:

1) As per BMC guidelines, consider providing a brief explanation of the importance and relevance of the study reported.

In accordance with the suggestion from the reviewer we extended the conclusion by providing the importance and relevance of the study.