Author’s response to reviews

Title: What is needed to guide testing for anorectal and pharyngeal Chlamydia trachomatis and Neisseria gonorrhoeae in women and men? Evidence and Opinion

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Response to the requests of Editor and Reviewers

INFD-D-15-00042 What is needed to guide testing for anorectal and pharyngeal Chlamydia trachomatis and Neisseria gonorrhoeae in women and men? Debate

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Dear Dr. Whiley

Thank you for your and Reviewers’ constructive comments which improve our paper. We have addressed these in a point-by-point reply below. Please let me know in case you have more questions.

Editor's comment:

You will note that reviewer 3 has raised questions over the approach used for this article, particularly whether “a systematic review” was conducted. I have sought clarification on this from the executive editor of BMC ID. The advice I was provided by the executive editor is that a systematic review is not required given this was submitted as a ‘debate’-type article. I do however have concerns over the length and focus of the article. My specific comments that need to be addressed are:

1. The word ‘review’ should be omitted from the title.
We have omitted ‘Review and Debate’ and replaced by ‘Discussion’.

2. The article is unnecessarily long and needs to be more concise.

We have shortened the paper in several sections, including all sections indicated by the Editor (below) and some additional sections. We also shortened the reference list and updated it with the most recent literature. At some places, we have added some information as suggested by Reviewer 2 (see below). Overall, the paper is shortened.

2a. The article should remain focused on what the current status of treatment is and how this can be improved. It seems to get side-tracked with other less relevant matters. Examples include: On page 5 the authors start talking about heterosexual men who are not within the confines of the paper.

The text on heterosexual men is considerably shortened, only a few sentences are kept as this group provides a reference for both women and MSM. Sentences now read: ‘Of note, MSM who define themselves as being heterosexual (e.g. male swingers) have appreciable numbers of anorectal infections as well [11]. Pharyngeal CT and NG prevalences in heterosexual men are similar to that seen in women [e.g. 11,28]. Overall however, data in heterosexual men are scarce.’

2.b. On page 6 under current management they discuss issues relating to NAAT performance and sampling.

We shortened this section as suggested and rephrased for clarity. Some sentences were added as was suggested by Reviewer 2, see below. The text now reads ‘Detection of extra-genital CT and NG is best done by NAAT [7]. Such tests are highly sensitive and specific and were shown valid and robust for extra-genital detection [e.g. 25,29,48-49]. Also, self-collection of samples in case of anorectal infections is well accepted and feasible in both women and in men. Still, the lack of clearance from the Food and Drug Administration (FDA-USA regulations) and lack of a CE-IVD mark (European regulations) for such testing, has greatly hampered its use in current clinical practice [50].’

2.c. Beginning Page 16, the section on “Other extra-genital STI” adds little weight and can be omitted.

We have rigorously shortened this section. Still, we would like to keep some text on this issue as it places the extragenital Chlamydia and Gonorrhoea discussion into perspective. Their presence may have implication for patient management (such as treatment). Also, lessons learned from these latter two infections may equally apply for other pathogens as well, which we believe is important to mention to the reader. This is becoming even more relevant as routine laboratory tests are becoming available that test multiple STI (e.g. MG, TV, CT and NG).
Now the text reads ‘As we have started to gain awareness of the occurrence of extra-genital CT and NG in women, we have been learning about other extra-genital STI as well. We know that Mycoplasma genitalium (MG), Herpes Simplex Virus, Human Papilloma Virus (HPV) and Trichomonas vaginalis (TV) can be found at the anorectal site in a woman. Presence at the anorectal site may be correlated to their presence in the vagina, such as has been shown for MG, TV and HPV [29, 89-91]. While some of these pathogens are routinely tested for at the genital sites of women, anorectal or pharyngeal testing of these STI is rarely done in practice. It is also not recommended or hampered when there are no available commercial assays (such as for MG). NAAT assays for the simultaneous detection of several anorectal infections ‘in one’ are being developed, and that perhaps may pose interesting future possibilities for combined extra-genital testing. The gaps that are revealed in the management of extra-genital CT and NG may also apply for these other STI. Further, detecting the simultaneous presence of different extra-genital pathogens will impact patient-management.’

Comment Reviewer #2:

This manuscript describes and discusses the information that is available, and more importantly not available, on extra-genital testing for Chlamydia trachomatis and Neisseria gonorrhoeae in men and women. It is an extremely useful document, is clearly written and well referenced and easy to read. I have no specific comments for the authors but have a few thoughts they might like to consider.

3. The authors make it clear throughout the manuscript that there is little known about the morbidity caused by asymptomatic infection at extragenital sites particularly for CT. However, I have been challenged following presentations on this subject about what evidence we have that CT in the rectum or throat are 'pathogens' when they are causing an asymptomatic infection. To my knowledge there is little or no evidence that CT strains causing asymptomatic infections at extra-genital sites are any different from genital sites. The authors may want to consider whether adding a phrase for the less informed reader that there is no evidence that CT strains from different sites differ in their pathogenic potential would be beneficial.

We agree that such information would be helpful to the reader and have added the following sentence ‘In fact, this is similar to genital infections, that are also frequently asymptomatic. There is little or no evidence that CT strains differ between anatomic sites regarding their genotype or their pathogenic potential.’ Also we added ‘.. and genital…’ in a later sentence reading ‘Even so, the large majority of extra-genital (and genital) infections in MSM and in women are asymptomatic ..’.

4. Page 6, lines 46-50: The sentence starting 'The lack of clearance...' is absolutely true. While many have adopted using these tests there may still be those that remain resistant to using
these tests without the appropriate regulatory procedures in place and the authors may want to consider following this sentence with a statement that good validation data is available and the tests have been shown to be robust or something similar.

We agree that it needs to be clear for the reader that the tests are valid and thus are perfectly fine to use. We have rephrased the section in order to be more clear. It now reads: ‘Such tests are highly sensitive and specific and were shown valid and robust for extra-genital detection [e.g. 25,29,48-49]. Also, self-collection of samples in case of anorectal infections is well accepted and feasible in both women and in men.’

5. Page 10: the discussion here around the additional cost of testing samples from extra-genital sites is interesting. In the UK, and I believe in Europe, there has been a number of studies initiated (but as far as I am aware not published) where multiple swabs from different sites have been placed or expressed into a single collection fluid for testing to reduce the cost. This is, of course, not covered by current FDA or EU approvals but it would be interesting to know if the authors have any knowledge of this or any experience of it and want to express this in the text.

The Reviewer refers to pooling of swabs. Indeed this could be potentially a cost-effective method, especially when prevalence is low, such as for pharyngeal CT/NG. Our group does at the moment not have data to confirm (cost-)effectiveness or feasibility for such pooling. As it is an interesting alternative, we have added a comment on pooling in the text ‘Another testing strategy potentially reducing costs is to test pooled multiple site samples. Such approach precludes feedback on the anatomic site(s) where the infection(s) occurs precluding treatment guidance, and its effectiveness needs to be further explored.’

Reviewer #3: This review discusses extragenital infections with chlamydia and gonorrhoea in women and compares published data in women with those from men who have sex with men. Could the authors indicate if this was a systematic review? The description of the search seems to indicate it was not systematic. Also it appears that a literature search was done for women but not formally for men who have sex with men who are compared with women.

The search was not systematic. However, we attempted to be as complete as possible by assessing all papers on the topic in women. All papers that contained information on anorectal Chlamydia were presented in Table 2, and also the authors were contacted for additional information (when information was not included in the paper) to assure that the Table was as complete as much as possible.

Kind regards,
Nicole Dukers-Muijlers

On behalf of all co-authors