Title: Is it time to switch to doxycycline from azithromycin for treating genital chlamydial infections in women? Modelling the impact of autoinoculation from the gastrointestinal tract to the genital tract

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Author's response to reviews: see over
Authors’ response to referees.

The authors would like to thank the two referees for their comments – our manuscript is much improved for them.

We detail our point-by-point responses below.

Referee 1.

This paper addresses an interesting and important point in the treatment of urogenital chlamydia infections in women. Although not many new data are presented, the paper is concise and raises the problem with great clarity. I have only one remark: in the last paragraph of the method section lines 81-85 it is stated: "A subgroup analysis of just those studies that did not measure doxycycline compliance found a very similar random effects pooled estimate for difference in treatment efficacy to the estimate when all studies were included (1.4% and 1.5% respectively) [3], suggesting that these values are sufficiently close to real-world ‘use-effectiveness’ for the purposes of our study." Shouldn't it on the contrary be that an analysis was done on those studies that DID measure compliance since those data are necessary for efficacy studies?

Authors’ response: We think that we have approached this correctly. Studies that DO measure compliance can exclude subjects that do not meet some level of compliance, and as such are likely to estimate a treatment efficacy that is higher than 'real-world efficacy'. Studies that DO NOT measure compliance will include patients regardless of their level of compliance, thus providing a better best measure of real-world efficacy. We have added some additional text to the Methods to explain this.

Referee 2.

Overall Feedback

The authors explore a question which definitely deserves greater attention in the age of increasing antibiotic resistance and waning treatment efficacy. The authors present a cogent narrative and the mathematical equations given are easily verifiable by a non-statistically minded audience. However, the article would benefit from an expanded introduction and greater clarification on the target population.

Major Compulsory Revisions

1. The second paragraph of the Background section seems to emphasize that the change from azithromycin to doxycycline should be made due to the probability for autoinoculation in women, but there is no discussion about this probability in men. Based on this background as well as the Study Objective listed in Line 69, it appears that the recommendations in this article are solely intended for women. If that is the case, the authors should explicitly outline this population in both the title of the manuscript as well as the abstract to ensure that the reader is clear who the recommendation is
intended to target. For example, this could be done simply by adding “in women” so that the title appears as follows: “Is it time to switch to doxycycline from azithromycin for treating genital chlamydial infections in women? Modelling the impact of autoinoculation from the gastrointestinal tract to the genital tract.” As stated previously, similar edits would be needed for the abstract.

Authors’ response: This is true, and we have updated the title as suggested and added 'in women' in two places in the abstract.

Minor Compulsory Revisions

2. The authors cite the Bachmann study in Lines 48-49 to indicate that the use-effectiveness with doxycycline seems to be high. However, it would be useful to explicitly indicate what percentage of patients cleared their initial chlamydia infection as is the case for lines 49-51. While the authors are correct in their assessment, the current wording does not allow the reader to judge for themselves what constitutes “high” without referencing the cited article.

Authors’ response: In light of point 7 below, regarding the addition of text concerning the Bachmann study to the Discussion, we have opted to remove this mention of Bachmann in the Introduction. We feel that this improves the flow of the manuscript while still giving appropriate attention to this important study.

3. There is a lot of white space in Figure 1 that may be unnecessary. It may be useful to revise the y-axis to 80% to 100% so that the confidence interval is a bit more explicit for the doxycycline group.

Authors’ response: We completely understand the reviewer’s concern about the large quantity of white space in the figure; however, we are concerned that changing the axis as suggested would distort and exaggerate the difference between the treatment efficacies. We would prefer to retain the 0-100% axis as used in the original submission.

Discretionary Revisions

Introduction

4. The authors may want to also include the meta-analysis by Lau and Qureshi entitled, “Azithromycin versus doxycycline for genital chlamydial infections - A meta-analysis of randomized clinical trials.” The Kong article is an important recent contribution, but the Lau/Qureshi article from 2002 shows how the conversation has evolved from equal efficacy of each drug in 2002 to potentially superior efficacy of doxycycline in the current treatment environment.

Authors’ response: We have added a mention of Lau and Qureshi to the Introduction.

5. Although the focus of the article is among women, there is another important study by Khosropour et al. called “Comparing Azithromycin and Doxycycline for the Treatment of Rectal Chlamydial Infection: A Retrospective Cohort Study” which would also add important information to the rectal
discussion in the first paragraph. Similarly, work by Hathorn et al. “What is the appropriate treatment for the management of rectal Chlamydia trachomatis in men and women?” would bolster this section a bit.

Authors’ response: We agree that these works by Khosropour and Hathorn articles are important, and indeed they were key motivations behind this study. However, they are two of several studies included in Kong et al.’s 2015 meta-analysis of treatment efficacy for rectal infections, and so we feel that it is not necessary to highlight them in particular.

6. Autoinoculation is defined in lines 56-57 implicitly, it would be useful to explicitly define this term in the text for individuals who may be external to the field but hold a cursory interest.

Authors’ response: We have added a definition.

Discussion

7. In the Discussion section, the manuscript may benefit from a greater discussion of medication reminders as 5 of the 81 individuals tested positive for chlamydia at follow-up in the Bachmann study. While the use effectiveness is high, it may be useful to discuss the need for providers to emphasize medication adherence given the fact that doxycycline is multiple doses instead of just one dose with azithromycin. This may be placed in the "common sense" bin, but I think it bears reiteration given the sub-optimal adherence levels.

Authors’ response: We have added an extra paragraph to the end of the Discussion to discuss Bachmann's study and this point in particular.