Author's response to reviews

Title: Timing of progression of Chlamydia trachomatis infection to pelvic inflammatory disease: a mathematical modelling study

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Author's response to reviews: see over
Dear Editor

Thank you for giving us the opportunity to submit a revised version of our manuscript “Timing of progression of Chlamydia trachomatis infection to pelvic inflammatory disease: a mathematical modelling study”. Please find below our point-by-point response, which is written in blue. Our changes in the manuscript are highlighted in blue. In addition, we have altered reference 13 as the manuscript is now published.

We would like to thank the reviewers for their positive initial remarks.

Responses to Referee 1:

Major Compulsory Revisions
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**Comment 1:** The authors state in the abstract that “progression at a constant from chlamydia infection to PID was most compatible with the findings of the RCT”. However, from the analysis carried out in the manuscript the “progression at the end of infection scenario” seems to be equally compatible with the RCT data as the constant progression scenario. Given the uncertainty and simplicity of the model I am not convinced that you can say one is definitely better than the other from the quantitative analysis carried out. It seems to me that the authors simply dismiss the progression at the end of infection scenario as being biologically unrealistic. Certainly PID in early infection seems to be ruled out by the analysis but various plausible “late infection” scenarios could work (e.g. as discussed in point 2) just as well or maybe better. Therefore, I think the authors are too strong in saying their analysis shows a constant progression to PID and they should include some more nuanced discussion/interpretation of their results.

**Response:** We agree that the evidence is not definitive. We have changed the wording in the Abstract (p2, Results) to ‘Progression at a constant rate from a chlamydia infection to PID or at the end of the infection was compatible with the findings of the RCT. The corresponding estimated fraction of chlamydia infected women that develops PID is 10% (95% confidence interval 7-13%) in both processes.’

And adapted the last sentence of the 1st paragraph in the Discussion section (p13),

‘The model estimates for the constant progression and progression at the end that 10% (95% CI 7-13%) of chlamydia infections progress to PID.’

We have rewritten the paragraph in the Discussion (p15-16) that considers the interpretation of the results to make is more nuanced.

**Comment 2:** Three simplistic PID progression scenarios are analyzed, two of which are unrealistic but represent bounds on the possible progression to PID. The most realistic scenario considered is a constant progression scenario in which women infected with chlamydia develop PID at a constant rate anytime during an infection. There are other scenarios that could also be plausible and at least should be discussed. For example, women may need to be infected for a certain time before than can develop PID, after which the rate of progression could be constant. Such a scenario is
likely to be a good fit to the RCT data, as it is between the constant rate and the end of infection scenarios in this study, and be particularly useful for determining the frequency/timing of testing for chlamydia and designing the implementation of screening to prevent PID (i.e. the time between tests for women should be less than this minimal time to prevent PID). Such a scenario could be explored with a modification of the model used and the authors may be planning to do this in future work. I do not think it is necessary to do this work for this paper but some discussion about such scenarios and how the results inform the implementation of screening interventions and what future work is required should be included.

Response: We agree that it should be clearer that other progression scenarios could also be plausible and should be investigated. We incorporated an additional model framework as a sensitivity analysis, where the mean time between start of infection and when progression to PID becomes possible can be varied, see Reviewer #2, comment 2.

We therefore have included in the Discussion the sentence (p13),

‘Other plausible possibilities about the timing of progression, e.g. assuming a woman has to be infected for a certain time period before being at a constant daily risk of developing PID, were not investigated because we did not have enough data to fit models with more than one unknown parameter.’

and changed the sentence about future work to emphasize that the timing of progression is still unknown (p16)

‘We plan to conduct future modelling studies that investigate the impact of achievable levels of chlamydia screening on the interruption of ascending chlamydia infections using a model that can also examine the effect of differences in the timing of progression.’

Comment 3: In the Discussion and conclusion section the implications of a constant rate of PID progression are discussed. It should be pointed out that a constant rate of progression in the model implies that the time between infection and developing PID follows an exponential distribution with a mean of 1/(rate of progression). This implies some women will develop PID soon after infection while others will develop PID very late in their infection. Such a distribution (if realistic) has implications for screening program design.

Response: Thank you. This is included in the revised Discussion on p15 (2nd paragraph), as follows, ‘In the constant progression scenario, the time window might be shorter than the duration of infection. The constant rate assumes that the time between start of infection and developing PID follows an exponential distribution. This implies that some women will develop PID soon after infection whereas others will develop it very late in their infection. In practice, there would always be some unpreventable chlamydial PID as the screening interval cannot be made short enough to find each infected woman before she progresses.’
Minor Essential Revisions

Comment 4: In Table 2. The sensitivity analysis for the parameter delta has parameters a=0 and b = 0.5. I think these should be a = 0% and b = 50% to be consistent with the baseline value.

Response: We have adapted this suggestion for Table 1.

Discretionary Revisions

Comment 5: One of the nice aspects of the work is the matching of the model to a RCT. The results from this RCT are discussed in the manuscript but I think it would make it easier to read the paper and interpret the modeling results, figures and tables if the results from the trial were more frequently displayed. For example data could be added to Figure 3 and Table 2 as well as various places in the text.

Response: We added a row with the results of the RCT in Table 2 and extended the column about the cumulative incidence of PID after one year with 95% CI. We also included in legend of Figure 3 the sentence ‘The observed cumulative incidences of PID after one year (%) in the trial were: control group 1.9 (95% CI 1.2 to 2.9), intervention group 1.3 (95% CI 0.7 to 2.1).’

Responses to Referee 2:

Major Compulsory Revisions (which the authors must respond to):

Comment 1: On page 14, you mention that “there are few mathematical modelling studies that consider timing and progression of PID”. I would argue that you haven’t really done this either. It seems to me that if you’re using the model to simply reproduce the results of the RCT, the strength of this type of analysis is not being used to its full potential. I mean, you’ve been able to determine that assuming constant progression to PID is most compatible with the results of the RCT. However for me, the immediate (and frankly more-interesting) question is: what is the average time of this constant progression?

Response: We apologise if the reviewer was confused. We actually said ‘There are very few mathematical modelling studies that consider explicitly how the timing of progression to PID might affect the outcome of chlamydia screening interventions [13].’ on p15. We clarified that we investigate in our study addresses the suggestion of Smith using the word ‘investigate’ in the Discussion on p15.

For the constant progression it is assumed that the mean duration between infection and developing PID follows an exponential distribution (as discussed in our response to Reviewer #1, comment 3).

We have added a section in Additional file 1 (p3) to clarify the different concepts about when PID occurs ‘How incidence of PID accumulates in each type of
progression.’ In the Methods section (p9) we explain this as follows,

‘Fourth, for each type of progression we used baseline values and the obtained maximum likelihood estimators to determine the time point since start of infection until half of the expected PID cases occurred (see Additional file 1 for more details).’

In the Results (p12), we say,

‘In the scenario of constant progression to PID, with a constant daily risk of developing PID, it takes 228 days until half of the expected PID cases are observed and for the progression at the end it takes 253 days, using the MLE in Table 2 (see Additional file 1 Figure A1). In the immediate progression scenario, it takes 0 days which is an intuitive consequence of progression without a delay.’

Comment 2: Scenarios 2 and 3 appear to be good starting points - in fact, scenario 3 may provide an upper bound on an actual numerical estimate, but I think adding a parameter representing the average time until PID in the “flow” between I_1 and I_2, and re-calibrating the model (and this new parameter). I think this would be a (relatively) easy modification to the model that would (in my opinion) significantly add to the content of the paper.

Granted, this will add an additional parameter to the model that is “difficult to observe”, however I believe that this is a tremendous benefit of analyses such as the ones you’ve performed here: they at least let us hypothesize about difficult to observe (or unobservable) phenomena.

Response: Thank you. We incorporated your suggestion of a model framework where the mean time between start of infection and when progression to PID becomes possible can be varied as a part of the sensitivity analysis. As we have only two data points and want to estimate the unknown fraction progressing to PID we cannot fit at the same time the parameter for the mean time between start of infection and when progression to PID becomes possible (see 2nd paragraph of Discussion on p13).

The detailed description of this model framework can be found in the Additional file 1 (p6) ‘Varying mean time between start of infection and time point when progression to PID becomes possible’.

We extended the Method section on p10 with

‘Third, we also explored varying the mean time between start of infection and when progression to PID becomes possible. We do this in a model framework similar to the constant progression scenario. An additional parameter \( \hat{f} \) is needed to specify the fraction of women who develop PID at the time point when PID becomes possible. This differs to the fraction \( f \) in that \( \hat{f} \) refers only to the women who remain infected at the time point at which progression to PID becomes possible. We did not fit this model with the additional unknown parameter to the trial data as we have only two data points. We derived maximum likelihood estimates for the fraction \( \hat{f} \) for fixed mean time between start of infection and progression to PID and report the corresponding fraction \( f \) (see Additional file 1 for more details).’
and the Result section on p12 with ‘In the additional model framework the corresponding best fitting values for the fraction of infected women developing PID ($f$) were in the same range as the main three types of progression (see Additional file 1 Figure A3).’

Minor Essential Revisions (which the author can be trusted to correct):

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METHODS

Comment 3: Model: Your model structure has an SIS natural history. Yet, there are several different equally-suitable model structures that could’ve been applied here (for example an SIRS, SIDRS - where “D” refers to a disease state, etc.). Why did you choose this particular structure? Did you explore alternative structures?

Response: We acknowledge that there is an ongoing discussion about the existence and duration of immunity after a chlamydia infection, e.g. in modelling studies it is typically assumed that there is no immunity after treatment. As mentioned in the Discussion section about the strength and limitations of the model there is a negligibly small percentage of women with repeated chlamydia infections since both the trial follow-up period and the baseline value for the mean duration of chlamydia infection were one year in this study (see response to Reviewer #3, comment 1). Therefore no recovery state was included. Since we were interested in the incidence of PID and assumed that a PID episode does not change the infection duration or future progression to PID we did not include a diseased state in our model.

Comment 4: Types of Progression: I found that having to read “constant progression” and “progression at the end of infection” a little wordy at times. It might be easier to simply define the progression scenarios (if you decide to keep them) in the Methods as “scenarios 1, 2, and 3”, and then simply refer to them by their scenario number.

Response: We acknowledge that the descriptions of the types of progression are a bit wordy. Some readers can be confused by numbered scenarios that are not described. On balance, we think it easier for the reader to be explicit which type of progression is meant.

RESULTS

Comment 5: Based on your AIC values, you state that all three types of progression are compatible with the RCT data. Were these values for AIC used to discriminate between the “viability” of the scenarios?

The reason why I ask is that based on a relative likelihood (using those AIC values), scenarios 2 and 3 are the least likely (comparatively speaking) to suffer from information loss:

For example: Scenario 1 vs. Scenario 3

$L(\text{relative}) = \exp[(\text{AIC}_\text{min} - \text{AIC}_i)/2] = \exp[(12.1 - 13.3)/2] = 0.55.$
Meaning that scenario 1 is 0.55 times as probable as scenario 2 or 3 to minimize the amount of information loss. In this case, I would say that from this point on you needn’t interpret, or even include scenario 1 from your discussion (even though you do say later that scenarios 1 and 3 are a little unrealistic).

From here, it would be a good place to include an analysis to estimate the time until PID.

**Response:** We used the Akaike’s Information Criterion (AIC) to compare the best fits (maximum likelihood estimators) of the three types of progression. We didn’t explore further possibilities to discriminate the scenarios as the point estimates of the trial have large confidence intervals, and the MLE are similar to each other and are all compatible with data.

We agree that the overall aim would be to estimate the time until PID occurs but as explained in our response to Reviewer #2, comment 2, we cannot estimate two parameters with only two data points. Analysing the time from start of infection until PID starts (using the date of diagnosis) requires the knowledge about when the infection in a woman started. This cannot be observed for ethical and logistical reasons and is therefore unknown as stated in the background section of the manuscript.

DISCUSSION AND CONCLUSION

**Comment 6:** On page 10, I am afraid that I do not follow the last paragraph: it seems to say that a constant progression (with a low fraction of those that develop PID) are most compatible with RCT results. However, I don’t quite understand the flow from this statement to your comment about “the need for infection to occur”. Isn’t infection already a given? Were there cases of PID where infection did not occur?

**Response:** We apologise if the reviewer was confused. We are unsure how to respond to this as we do not use the phrase as quoted.

The first three paragraphs of the Result section describe how the three types of progression behave for varying fraction progressing to PID. We hope that referencing to Figure 2 and using the word ‘predicted’ throughout the first three paragraphs of the Result section on p10-11 and replacing the word ‘predicted’ with ‘corresponding’ respectively ‘estimated’ in the 4th paragraph will help. Additionally, we adapted the title of Figure 2 and rewrote the result about the scenario of progression at the end (p11).

**Comment 7:** On page 11, at the start of the second paragraph, you state that: “Table 2 shows...women who progress to PID where the observed cumulative incidences are considered.” I’m a little confused by the qualifier, “...where...incidence is considered.” Were there scenarios you investigated that did not consider cumulative incidence?

**Response:** The first part of the Result section describes how the three types of progression behave for varying fraction progressing to PID, see Reviewer #2,
comment 6. To clarify that Table 2 shows the MLE result using data from RCT we rephrased the sentence (p11) ‘Table 2 shows the maximum likelihood estimator (MLE) and the corresponding 95% CI for the estimated fraction of chlamydia infected women who progress to PID, using the observed cumulative incidences from the trial.’

Comment 8: On page 13, you begin to discuss the limitations of the RCT data. While I think it’s important to do so, I also think that it is a little redundant - since these would have been discussed in the original article.

I would qualify this paragraph with something like: “There are also limitations to the RCT data. Although discussed previously [reference], we restate limitations as they apply to our study here.”

Response: We have included the sentence “Although discussed previously [11], we restate limitations as they apply to our study here.” on p14.

Comment 9: On page 14 (last paragraph) you mention the discrepancies between your findings and the findings using animal models.

While I agree that rodent models of chlamydial genital infection have been extremely valuable in helping us learn about many aspects of the natural history of infection (for example the immune mechanisms that resolve infection, provide resistance to re-infection, and that may be responsible for clinical disease), their main purpose is for inferential analyses of C. trachomatis in humans, not for direct comparison.

There are several important (and fundamental) differences between mouse and human Chlamydia infections that are frequently overlooked. In the case of progression to PID, there are equally significant considerations related to allometric scaling of life history traits and metabolic rates that will contribute to the observed discrepancy between the “time until disease” for rodent and human genital infections.

If we use the duration of infection in murine models of Chlamydia as an example, they repeatedly demonstrate that infection is resolved within 28 days. When compared to the life history (i.e., longevity) of a laboratory mouse (which is roughly 575 days), the average duration of infection represents nearly 5% of their lifespan. Human infections, in contrast, last on average of 1.25 years, but can last as long as 4 years. This longer estimate represents approximately 5% of the 80.4 years of a person’s life expectancy in Canada.

Therefore, as a point of departure it seems reasonable to propose that since there are differences in scale between the duration of infection, other natural history parameters such as the “average time until PID” should also approximately scale between host species. In light of your current results, policy estimates inferred from short, animal-derived times until PID might not suitably map onto the biology of human Chlamydia infections or capture the fundamental dynamics of its epidemiology over time in the presence of policy interventions.
Response: We agree that chlamydia infection in mice cannot directly be compared with the infection in human and therefore added in the revised Discussion about the immediate progression the sentence ‘It is possible that *C. trachomatis* ascends early in the course of infection in humans but that clinical PID is observed later.’ on p16.

Responses to Referee 3:

Comment 1: The main issue for me is ensuring that the approach is modelling the progression to PID as direct effect of genital chlamydia and not other microorganisms... - this is mentioned in the results. The authors also briefly mention repeat infections - we know this can influence progression and I note their argument for not including but I would want to be re-assured that this is sufficiently robust?

Response: In the model using baseline values ~0.2% of women in the control group experience a second infection within the follow-up period of one year and in the intervention group only ~0.06%. If a repeated infection with chlamydia increases the risk of progressing to PID we would speculate that the estimated fractions progressing would be too high as we assume in our model experienced PID episodes having no influence on the risk of future PID episodes. In the RCT there is no case reported where a woman reported two PID diagnoses within the follow-up period.