Reviewer's report

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

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Reviewer: David Vickers

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In my opinion, this is a tremendously valuable article, because it contains an interesting and unique data-model combination for modelling the progression of chlamydia infection to pelvic inflammatory disease.

For me, an effective framework for applying, what is called, “Systems Thinking” is key to developing models that achieve a particular purpose, provide insight, and will have a positive impact on policy. And from the analysis you’ve performed in this manuscript, I think this is well on its way to doing so.

Having said this however, I did find the article quite difficult to follow at times, and I also thought that parts of the analysis were incomplete. Overall, I think there are several major points to be clarified, as well as some additional analyses that need to be performed (or at least discussed as topics of future research). I am hopeful that you will consider including some suggestions.

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

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?

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.

3. 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.
Minor Essential Revisions (which the author can be trusted to correct):

METHODS

1. 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?

2. 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.

RESULTS

1. 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 sat 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.

DISCUSSION AND CONCLUSION

1. 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?
2. 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?

3. 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.”

4. 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.
Level of interest: An exceptional article

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests.