Reviewer's report

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

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**Reviewer:** Richard Gray

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Screening for Chlamydia trachomatis to prevent pelvic inflammatory disease (PID) is an important public health strategy for sexually active females. The work presented by the authors uses simple mathematical modeling to infer the proportion of women with chlamydia who develop PID and the likely process of progression to PID. This information is useful for the design of screening programs and understanding the morbidity associated with Chlamydia trachomatis infection.

The work is novel in that a simple SIS model of chlamydia infection is matched to clinical trial data to infer important characteristics of PID progression that cannot be estimated through epidemiological studies due to ethical and logistical reasons.

The manuscript is well written, the analysis carried out is suitable to answer the research questions and the mathematical analysis appears to be correct.

I think the paper is suitable for publication in BMC Infectious Diseases but I do have some concerns with the interpretations of work and the PID progression scenarios investigated.

**Major Compulsory Revisions**

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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.

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 the 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.

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.

Minor Essential Revisions
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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.

Discretionary Revisions
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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.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

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