Sharmistha Mishra
MAP Centre for Urban Health Solutions
Li Ka Shing Knowledge Institute
St Michael's Hospital, Unity Health Toronto
University of Toronto
sharmistha.mishra@utoronto.ca

Dr. Yiming Shao & Dr. Jianhong Wu
Editors-in-Chief of *Infectious Disease Modelling*

Re. IDM-D-20-00064

Dear Editors,

Thank you for considering our manuscript entitled *Contribution of high risk groups' unmet needs may be underestimated in epidemic models without risk turnover: a mechanistic modelling analysis* for publication in Infectious Disease Modelling.

We are very grateful to the reviewers for their helpful comments, and we endeavoured to address all of them with appropriate revisions. We attach here a detailed description of our changes and additional comment to explain/justify our editing decisions. We hope that with these edits, you will now find the manuscript acceptable for publication, as suggested in your previous letter.

Thank you again for your consideration, and we look forward to your response.

Sincerely,

Jesse Knight and Sharmistha Mishra
on behalf of co-authors

Reviewer #1

Due to have no vaccination for STIs, or persons are not immune to STIs after infected with sexually transmitted diseases, it should consider that STIs have no herd immunity.

We agree that the choice of terminology, "herd immunity" is confusing, especially since we have simulated a "treated", rather than "immune" group as the final health state. So, we've replaced the phrase "herd immunity" with "herd effect" throughout the paper. However, herd effect underpins one of the three key phenomena explored in the paper, and notably it relies on the existence of a treated/immune group, as distinguished from herd effects associated with high infection prevalence (partnerships between two infectious individuals resulting in no transmission). Specifically, it is not possible for reduced herd effect due to loss of infectious individuals via turnover to increase prevalence, whereas reduced herd effect due to loss of treated/immune individuals can and does increase prevalence due to re-supply of infectious individuals. To clarify this point, we've also added to the discussion:

First, we did not capture the possibility that some individuals may become re-susceptible to infection after treatment – an important feature of many STIs such as syphilis and gonorrhoea [Fenton2008]. As shown by [Fenton2008] and [Pourbohloul2003], the re-supply of susceptible individuals following STI treatment could fuel an epidemic, and so the influence of turnover on STI prevalence and tPAF may be different. In fact, the herd effect underpinning phenomenon 2 relies on the existence of a treated/immune health state, since only net replacement of treated (versus infectious) individuals with susceptible individuals via turnover can increase prevalence in the high risk group as observed.

We chose to simulate a "treated" health state after this study grew out of HIV modelling work, but we did not call the simulated infection "HIV" since we did not model infection-attributable mortality. We note in the methods (§ 2.2) how the infection could also represent hepatitis B virus, and indeed we think our insights may be useful for a variety of non-STI pathogens where risk heterogeneity is present, many of which may have at least temporary/treatment-induced immunity.

The most effective prevention is a substantial reduction of sexual partners and/or expanded condom use for STI. This should be considered in the manuscript.

In the discussion, we have added the following details to help clarify the types of interventions which may be most affected by the insights from the paper:

For example, epidemic models which fail to include or accurately capture turnover may underestimate the importance of addressing the unmet needs of key populations at disproportionate risk of HIV and other STIs, such as gay men and other men who have sex with men, transgender women, people who use drugs, and sex workers. Such needs may be addressed by interventions tailored to the unique vulnerabilities experienced by key populations, interventions such as enhanced and prioritized screening and testing, condom use programmes, and reductions in barriers to safer sex.

Reviewer #2

1) How is the turnover effect on the medium risk group? As it may have various effects on this group which usually has the largest population and could impact the overall disease pattern.

We agree that medium risk group(s) undoubtedly play an important role in the transmission dynamics of STI, especially in the context of turnover. However, our aim in Experiment 1 was mainly to examine the mechanisms by which turnover influences equilibrium prevalence. To do so, we described the three mechanisms in the context of the highest and lowest risk groups, such that their relative influence on higher vs lower risk groups could be appreciated. For example, phenomenon 1) describes the net movement of infectious individuals from high to low risk; while phenomenon 2) concerning reduced herd effect with greater turnover has the largest impact on the highest risk group. By contrast, phenomenon 3) the number of partnerships with infectious individuals influences all risk groups equally due to assumed proportionate mixing. Thus, we feel that describing these mechanisms in the context of the medium risk group would not add significantly

to the readers' understanding of the mechanisms. In fact we are concerned that some confusion may arise in trying to communicate the balance of mechanisms in the medium risk group, which may ultimately be subject to the specific assumptions of risk group size and relative contact rates, as compared to the more simple cases of the highest and lowest risk groups.

We do acknowledge that the rationale described above was missing from the paper, and that essentially no mention was made of the medium risk group in Experiment 1 results. As such, we have updated the results § 3.1 with the following:

To explain the inverted U-shape and different turnover thresholds by group, we examined the processes contributing to prevalence, first in the high risk group, and then in the low risk group. Prevalence in the medium risk group is then driven by a combination of these processes; as such, we don't detail the processes in the context of the medium risk group.

We also added to Figure 5 the three panels for the medium risk group, and the following sentence to the end of § 3.1.2:

The effects of these phenomena on the medium risk group were a mixture of the effects on the high and low risk groups, as illustrated in Figure 5d–5f, leading to the unique profile shown in Figure 4b.

2) Please illustrate the Figure 5 in more details, i.e. what are the different scenarios for panels in each column. Formulas for the curves may help readers to understand more.

To clarify what is being plotted in Figure 5, we've revised the methodology for Experiment 1 (§ 2.3.1) to update the text and to include formulae for the plotted quantities, new Eq. (5). We think this is what the reviewer requested, versus closed-form solutions for the plotted lines; the latter could be quite difficult to obtain and we think might be beyond the scope of the present work. To further improve the ease of understanding Figure 5, we also made the following changes:

- added panel row and column headings at the left and top, respectively
- removed the legend from each panel and replaced it with a single legend at the top of the entire figure
- added a red shaded area below zero labelled "net loss" and labelled the non-shaded area above zero "net gain"

We hope that these changes address the limitations noted by the reviewer.