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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 thank the reviewers for their helpful comments and suggestions. We endeavoured to address the reviewer comments with appropriate revisions, and provide a point-by-point response to each comment and suggestion. The reviewers' suggestions were helpful and we believe have helped improve the paper.

We look forward to your review and consideration of the revised manuscript for publication.

Sincerely,

Jesse Knight and Sharmistha Mishra
on behalf of co-authors

Reviewer #1

This is a well design study which used turnover between risk groups to do modelling for projecting the transmission population attributable fraction. There included three phenomena that drove shifts in equilibrium sexually transmitted infections (STIs) prevalence across risk groups at variable rates of turnover: 1) net flows of infectious individuals from high risk groups into low risk groups; 2) changes to herd immunity, especially within the high risk group; and 3) changes to the number of partnerships available with infectious individuals. My suggestions are the following:

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. The "treated" group are mechanistically considered an "immune" group, in that following treatment individuals are no longer susceptible to infection or re-infection. The "treated" group therefore, contribute to herd effects as they would in a classic S-I-R model (susceptible-infectious-recovered) since the R in this case is mechanistically equivalent to the treated compartment. Thus, for clarity, we have replaced the phrase "herd immunity" with "herd effect" throughout the paper. To clarify this point, we have 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.*

Although we specifically examine the question of turnover in the context of an STI, our findings may also be useful for non-STI pathogens which follow an S-I-R natural or treatment-mediated biological course. We have added the following to the limitations section to help clarify the transferability of insights:

> *Moreover, our findings are likely relevant to non-STI pathogens when risk heterogeneity is present, many of which have natural or 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 to provide further context with respect to interventions, and cited the 2016 WHO guidelines for HIV prevention and treatment interventions for key populations.

> *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. That is, epidemic models without turnover may underestimate the potential impact of prioritizing, allocating, and tailoring interventions for key populations: interventions such as enhanced and prioritized screening and testing, early diagnoses and treatment, condom use programmes, and reductions in structural barriers to safer sex [WHO2016].*

Reviewer #2

The authors explored the role of turnover in evaluating the transmission dynamics of infectious diseases, especial STI. A multi-group model incorporate with data-guided framework is used to exam this effect. The authors numerically show the importance of considering turnover to evaluate the disease transmission in different risk groups via three study cases. This topic is interesting. I have the following comments:

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.

First, in our analyses, the largest risk group was the low-risk group. We have thus clarified in two locations the relative size of the groups: in Methods 2.2:

> high H *(smallest)*, medium M, and low L *(largest)*.

and in Results 3.1:

> first in the *smallest* high risk group, and then in the *largest* low risk group.

Second, our rationale for focusing on the highest-risk group was guided by the framing of research questions around key populations who are often represented in HIV/STI transmission modelling as the highest risk group, and for whom tPAF are now increasingly being measured. The highest-risk group therefore represents a well-demarcated group (epidemiologically and with respect to programmes) that can be identified for population-specific programming, and on whom tPAF are now increasingly measured. We therefore focused the mechanistic examination (Experiment 1) on the highest risk group as the explanation for the main research question on the influence of turnover on tPAF of the highest-risk group.

We agree with the reviewer that it will be important to further study how turnover mechanistically influences the prevalence and tPAF of the medium risk group. However, we feel that such an examination is beyond the scope of the current study. answers would require a new research question and specific experiments wherein the focus is on the influence of turnover in the medium-risk group – but examination which would benefit from future study. For example, the prevalence ratios involving the medium risk group were not strictly monotonic, so the potential influence of turnover on the tPAF of the medium risk group would actually depend on the rate of turnover. Similarly, while the contribution of the medium risk group to onward transmission would likely increase relative to the low risk group, the contribution would likely decrease relative to the high risk group; thus we cannot reliably conclude that the medium risk group tPAF would increase or decrease, overall in the presence of turnover.

In the meantime, we have added the following in the revised manuscript to address the comment and suggestion. Results 3.1:

> 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.*

We also added to Figure 5 the three panels for the medium risk group, and the following sentence to the end of Results 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 have revised the methodology for Experiment 1 (Methods 2.3.1) to update the text and to include formulae for the plotted quantities: new Eq. (5). 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.