Done:

* Edited description of assortativity coefficient for clarity
* Added more description of initial conditions
* Described model parameter units in methods
* Added figure to show proportion latent as R0 varies in SLIRS model.

MAJOR TO DO

* Edits to analysis of simulation analysis
  + male bias calculation – recovered class instead – easier to explain (just describe as notification rates of recently diagnosed/treated individuals)
  + Add relapse and see if results in increased sex bias (more men with previous TB). Show figure in supplement
  + **~~Redo simulation study with 1 initially infected individuals~~**
* Check for papers describing sex differences in duration of latent infection
* Spelling mistake in line 29 page 5??
* Introduction:
  + Citations saying little difference in # of contacts by sex
  + Citations for PARAGRAPH 3 INTRO about where transmission of TB occurs (shared air settings)
* Discussion:
  + Limitations paragraph: Population size/incidence rates & FAST SLOW TB
  + Paragraph about application of this model to data? REVIEWER 1
* Add/update citations!

ASK JOHN:

* Review 2 comment about figure 2 caption (Should we change figure? I think they are confused by white boxes showing where MF bias is around 1.8).

Re: Resubmission of *Effects of assortative mixing and sex-traits on male-bias in tuberculosis: A modelling study*

Dear Editor,

Please find enclosed with this letter our revised manuscript “Effects of assortative mixing and sex-traits on male-bias in tuberculosis: A modelling study” which we resubmit for publication as a research article in *Royal Society Open Science*.

**Editor Comments**

The paper reviewed favourable comments from both reviewers and found the sex-bias aspects of this paper particularly interesting. However, besides a number of comments from the reviewers that need to be addressed, serious concerns relating to the link of the present studies with a simulated TB were raised. A reviewer suggested the following  
'I strongly recommend that the authors remove the references to TB, and instead expand the more theoretical components of the work and/or choose an alternative example infection that can be better represented by the model structure chosen.'  
  
We would like you to consider this comment in particular and would accept a resubmission.

**We considered reviewer comments carefully. We addressed a number of the larger concerns, including adding a paragraph about the applicability of study to real systems in the discussion to address Reviewer 1.**

**We have also considered comments from Reviewer 2 carefully and have added text in the manuscript to reiterate that reactivation, reinfection, and fast-slow disease progression are not included in the model, and these dynamics are important when trying to model population-level disease dynamics (CITE Reviewer papers). However, the focus of our study was not on population-level disease dynamics but on network structure, sex-specific disease rates, and resulting sex-bias.**

**In reality, there have been few studies that actually propose that there are sex-specific differences in reactivation, reinfection, and fast-slow disease progression by sex and therefore we don’t see how they could change our results. This model is a simplification of TB and we have added more discussion about the ways it is a simplification, but we feel the Reviewer has overstated their assertion that these simplifications will bias our results since there is no evidence that these rates vary by sex.**   
   
  
**Reviewer 1**  
  
Comments to the Author(s)  
Spelling mistake in line 29 page 5  
  
Would like a short paragraph in the discussion to mention if this model could be **expanded and applied to real epidemiological data from specific populations or locations to determine the impact of the factors discussed in the paper on the observed sex bias.** Or any other potential way to expand this model to use actual data to determine to quantify the extend to which behaviors, socioeconomic, cultural factors influence sex bias.

**PLAN:**   
  
Reviewer: 2  
  
Comments to the Author(s)  
The manuscript uses a theoretical SLIRS network model to explore the effects of differences in infectivity, susceptibility, disease duration, and assortative mixing on sex-bias in the incidence of infection. This aspect of the work is potentially interesting, and, while none of the results are unexpected, if fleshed out it could provide a useful indication of the magnitude of the sex-bias that may result from different combinations of parameter values.  
  
The authors also attempt, however, to link the work to a specific disease, tuberculosis, that has a strong sex-bias. This component of the work is poor and greatly overstates its conclusions, as the simulated disease bears little resemblance to tuberculosis. While the authors do say in the discussion that ‘these simplistic models do not fully capture the complexities of TB’, the model does not even capture basic elements of tuberculosis epidemiology, in ways that could greatly bias the results.

I strongly recommend that the authors remove the references to TB, and instead expand the more theoretical components of the work and/or choose an alternative example infection that can be better represented by the model structure chosen.  
  
Things missing /wrong about the representation of tuberculosis include (and this is not a comprehensive list):  
  
1) The model does not allow people to re-develop TB after they have recovered (the R->S transition in the model is designed to represent the birth of new susceptible individuals). In reality, rates of TB are far higher among people who have previously had TB than people who have not (due to both reactivation and reinfection). This will have led to their model underestimating the sex bias, as it has not captured the amplification of the sex bias due to the higher proportion of men with previous TB.

**PLAN: We included reactivation in the model (R->I transition) with a rate of \_\_\_ (CITE). It did not result in underestimation of sex bias (shown in supplement FIGURE). We updated text to reflect new result.**

2) The model does not include fast and slow progression to disease. Following infection with Mtb, there is a high risk of progression to disease of around 5-10% in the first two years, followed by a much lower risk of progression in subsequent years. Previous work has shown that models that do not incorporate these varying progression rates “provided poor fit to the empirical evidence” (Menzies, Nicolas A., et al. "Progression from latent infection to active disease in dynamic tuberculosis transmission models: a systematic review of the validity of modelling assumptions." The Lancet Infectious Diseases 18.8 (2018): e228-e238.)  
**We agree this aspect of our model is a large simplification of TB dynamics and if we were trying to fit a transmission model to time series of real incidence data for a specific population we would need to include more complexity and population-specific parameter rates. However, we feel this assumption is valid for the purposes of this study for two reasons, (1) the vast majority of notified cases are recent infections – i.e., “fast” TB – rather than reinfections and reactivation (CITE). We assumed the latent period was 10 months on average (this is related to comment 4) so our simulations explicitly model “fast TB”. And (2) the focus of the study was not fitting to cumulative incidence data as was the focus of Menzies et al. Rather we were interested in a simpler question about whether assortativity can help explain excess TB among men. If we wanted to fit models to data from a specific population, we would take a different approach and including fast-slow TB would be more important.**

3) Linked to 2, the model does not include reinfection, or protection against reinfection, in people who have been infected but not yet developed disease. People with latent infection can be reinfected, which can put them at higher risk of progression to disease than someone with a more remote infection. Prior infection provides some infection against reinfection however. Not including reinfection and protection against reinfection will have altered the estimated sex bias, although without explicitly modelling it, it is difficult to determine how much and in which direction.  
**Related to 2 and 4, our simplistic model explicitly considers “fast-TB” and the likelihood of being reinfected over this short time scale is low (CITE). As a result, we think including reinfection in the model would have negligible effects on estimated male-bias.**

4) It is not at all clear what parameter values were used to represent TB (the full ranges shown in Table 1, or specific values within those ranges? And no units are given for the rates. Are they per year?), and so it is not possible to evaluate whether the parameter values were appropriate.

**We only simulated models with the specific values listed in Table 1 (not ranges within values listed). The parameter units are in months. We edited descriptions of model parameterization in the methods sections with rationale for those specific values and rates.**   
  
5) They varied the simulated R0 for TB from 0.5-3.5, but it doesn’t appear that they allowed the proportion of the population with latent infection to vary alongside that, keeping it constant at 23% (I think, it is not clear). The empirical estimate of 23% of the population having latent infection is a global estimate, with by county values varying from <<10% to >50%. Unless the proportion of people with latent infection that the model is calibrated to is varied in a sensible way with R0, then the fitted parameter values will be completely unrealistic.

**The proportion of the population with latent infection varied with R0. We added a figure in the supplement to show how the proportion latent at equilibrium changes with model parameters in SLIRS model. We removed confusing text describing the 23% value which we used to in preliminary simulations to figure out transmission rates and latent periods that lead to 23% of the population being infected at equilibrium but in the end we considered higher and lower transmission rates and set the latent period at an average of 10 months.**  
  
6) The model has a population size of 1000 only. Given that the annual estimated incidence of TB reaches a maximum of only around 0.6/1000 in the country with the highest incidence, with incidences being far lower in the majority of the world, the simulated population size is far too low to provide meaningful results (if realistic incidences were simulated).

**Outbreaks in specific sub-populations can reach higher incidence rates that populations as a whole – for example, in neighborhoods, homeless populations, or a ships** [**https://academic.oup.com/milmed/article-abstract/155/8/347/4847570**](https://academic.oup.com/milmed/article-abstract/155/8/347/4847570)**). However, our model was not designed to represent any specific population or subpopulation and the choice of this population size was a matter of computational resources (other studies of epidemics on networks use similar population sizes CITE SALATHE, SAH?). Our aim was describe how male-bias can be generated and we don’t think our main results about assortativity leading to male bias will change if larger population sizes were used.**   
  
7) The authors say that “We quantified male-bias as the number of infected males divided by the number of infected females”. This is inappropriate for TB, as the number of people who are infected and the number of people who have disease vary greatly, and the empirical data that are available on sex bias (and that the manuscript cites), all refer to sex bias in disease incidence, prevalence, or notifications. Given all the limitations given above, it may not make any difference in the results for the model used, but in a model that more accurately represents TB, the sex bias in infection will be different from the sex bias in disease  
**We agree this was a confusing aspect in the submitted draft. We edited text in the “general approach section” to steer readers to where male-bias is explained in the “analysis section”. We updated calculations in light of this comment. Male-bias for all models is now calculated as number of individuals in the R class at the end of the simulation (could be thought of as “notification” of recently diagnosed/treated individuals).**

Other comments:  
  
Reference 17. State the study setting in the text

**Stated “In Uganda” when referencing study.**  
  
Page 3, lines 11-20. The studies cited describe numbers of close contacts-usually people who respondents exchanged at least 3 words with face-to-face. These contacts are relevant for close contact droplet infections. Mtb is airborne however, and the relevant contacts are people who the respondent ‘shared air’ with indoors. These include, for instance people on public transport with the respondent, and the variation by sex may be different for these contacts are for close contact.

**Reviewer is saying there may be differences in the number of adequate contacts between males and females, even if the number of close contacts (>5 min) is similar, because of sex-differences in ‘shared air’ settings (e.g., public transport). We agree, and we substantially edited paragraph to reflect this idea.**

Figure 2: ‘Only parameter combinations leading to mean M:F case bias greater than 1.1 are colored and the white boxes show parameter combinations leading to a mean M:F case bias from 1.7 to 1.9’ – this does not make sense  
**We edited text in figure caption to hopefully improve understanding. (ASK JOHN ABOUT HOW TO RESPOND).**

As I understand it, the variation in the boxplots in Figure 4 and 5 represents the variation between the results from different model runs. As an arbitrary population size was chosen (1000), this variation is meaningless. Instead, a combination of a larger population size and/or more model runs should be used, and only the (stable) mean result shown.  
**Responding as if Reviewer is referring to figures 3 and 4. (ASK JOHN ABOUT HOW TO RESPOND).**

How is infection seeded into the model? With small R0s and sex assortative mixing, the sex of the people seeded with infection is likely to have an effect on the results.

**In paragraph before the Analysis subsection in Methods, we edited to include initial conditions.**  
  
Reference 5: either the Global TB report and/or Horton et al would be better here (Horton, Katherine C., et al. "Sex differences in tuberculosis burden and notifications in low-and middle-income countries: a systematic review and meta-analysis." PLoS medicine 13.9 (2016): e1002119.)  
  
The talk of "male-bias" in this first paragraph is slightly confusing since sometimes it is used it to refer to burden of disease and sometimes access to care, without specification. And when it's used to refer to access to care, it's not quite clear whether it's a male advantage or disadvantage.  
  
“For instance, males are more likely to spread infection to their contacts than females (12,13), indicating higher male transmissibility.” The data are less clear than this statement suggests. Dodd et al isn't a good ref, since it's attributable to higher prevalence in men (rather than individual infectiousness).  Neither Peru (Grandjean 2015) nor Karonga data (Guerra-Assunção 2015) show any difference in disease among household contacts by index case sex. But older data from the Netherlands found more secondary cases for male indexes (Borgdorff 2001) (like the Hector paper cited in the manuscript).  
  
“Finally, the length of time from disease to treatment can vary by sex, with males generally delaying care for longer period than females (14)”. Again, this is a strong statement to make based on a single study, with the WHO report or Horton et al providing better evidence  
  
“Whether biological sex-traits or assortative-mixing by sex, have an outsized effect on male-bias at the population-level is the focus of this modelling study”- what about socio-behavioural factors (e.g. smoking, alcohol, care seeking behaviour)  
  
“Meta-analyses and reviews present strong evidence that there may be differences in immunity and infection for TB between males and females (3,4,15,30)” 3 and 4 are neither meta-analyses or reviews  
  
“With regards to transmissibility, the proportion of infections caused by males was estimated to be 1.3 to 1.8 times higher than infections caused by females in South Africa and Zambia (12).” The paper says nothing about transmissibility. The difference is due to difference in the prevalence of disease between men and women  
  
“and whether and how the infectious period could vary between sexes is an open area of work” – citations, e.g. Horton, Katherine C., et al. "A Bayesian approach to understanding sex differences in tuberculosis disease burden." American journal of epidemiology 187.11 (2018): 2431-2438.  
 

These results are original not under consideration for publication elsewhere. All authors have approved the attached manuscript for submission.

I can be reached by email (paigemiller554@gmail.com). Thank you for your consideration.

Sincerely,

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