Heterogeneities in individual-level infection are more important than social mixing patterns in driving male-bias for human TB

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**Study narrative**: Across the world, more cases of TB are reported among men than women. Hypotheses for this pattern include differences in social mixing patterns in social networks and infections of men and women. We wanted to understand the potential impact of social mixing patterns (assortativity) and heterogeneity in the infection process (susceptibility, transmissibility, and infectious period) on sex-bias in TB cases. We wanted to learn this because the relative potentials for previous explanations for sex-bias have never been systematically assessed alongside each other in a model. Also, understanding drivers of male-bias might inform future epidemiologic research and public health control strategies. To determine the relative effects of mixing patterns and individual-level differences in infection, we conducted a comparative simulation study of three pathogen scenarios spreading on networks that varied from random to extremely sex-assortative. Pathogen scenarios included heterogeneities in susceptibility, transmissibility, and infectious period by sex. We found no evidence that preferential-mixing by sex can drive male-bias in TB alone, even with extreme levels of sex-assortativity. Instead, heterogeneities in infection and transmission by sex alone or combined with sex-assortativity can lead to realistic levels of male-bias observed globally. While individual infection and transmission affect who gets infected, how many infections and overall epidemic dynamics were mostly unchanged by the presence of these sex-specific differences.

**Intro outline:**

Territory: TB and male-bias in infections

This paragraph establishes the widespread nature of TB and male-bias in TB cases globally.

Niche: Mechanisms promoting male-bias in TB

This paragraph reviews proposed mechanisms for male-bias: bio-behavioral mechanisms which alter infection and transmission and social which alter exposure to Mtb.

Occupy niche: Model to assess relative importance of assortativity and heterogeneity in infection by sex in driving male-bias

This paragraph indicates a focus in previous research on single mechanisms and thus a research gap comparing the relative importance for different mechanisms to drive observed levels of male-bias.

This paragraph outlines our study goals, hypotheses, and methods.

**Methods:**

This paragraph describes the process of generating synthetic social networks for TB transmission experiments.

1. To simulate synthetic, human, social networks, scale-free graphs with a mean degree of 10 and preferential attachment parameter X.

This paragraph gives the details of re-wiring algorithm which was used to produce assorted networks.

1. To generate variation in sex-assortativity of synthetic networks, sex was randomly assigned to nodes and a re-wiring algorithm was developed whereby edges occurring between-sex were randomly replaced with edges occurring within-sex until the desired level of assortativity (measured by Newman’s discrete r) was reached within a small range of error .

This paragraph describes the SLIRS model and variations used to compare results with different variations of this model.

1. To simulate the persistent spread of TB in a social network of a high TB burden area, we used a Susceptible-Latent-Infectious-Recovered-Susceptible (SLIRS).
2. To understand how assumptions about TB transmission affect male-bias results, we performed sensitivity analyses with SIR, SLIR, and SIRS dynamics and three levels of transmission .

This paragraph explains how individual-level heterogeneity in infection and transmission were incorporated into disease model.

1. To understand the relative effects of assortativity on male-bias compared to heterogeneity in infection by sex, three separate models were created with a varying ratio of male to female susceptibility (), transmissibility (), and infectious period ().

This paragraph explains how we assessed male-bias in simulations and compared simulations to real data from WHO.

1. To measure male-bias, we calculated the number of males infected over the course of the epidemic for SIR and SLIR model structures and as the equilibrium ratio of male to female cases in the SIRS and SLIRS model structures.

This paragraph explains how we compared epidemic dynamics.

1. To measure the effects of assortativity and heterogeneity in individual-level infection on epidemic dynamics, we calculated the total outbreak size, epidemic duration, equilibrium latent and infected prevalence for each simulation.

This paragraph describes how our model output compares to real-world estimates of prevalence LTBI and incidence of TB cases.

1. To understand model output in relationship to real data, prevalence of latent infection were assessed with information in the 2018 WHO TB Report. In 2017, 1.7 billion people (23% of the world’s population) were estimated to have latent TB infection.

**Results:**

This paragraph provides statistics of assorted networks created with re-wiring algorithm.

* The re-wiring algorithm produced networks of desired levels of assortativity () which has a tight linear relationship (Fig 1) with modularity (). All networks produced were connected (one component) and simple (no loops or multiple edges).
* At higher level of assortativity, there are considerable increases to network statistics that could affect epidemic dynamics (Fig 2): clustering (nearly 3 times baseline), degree assortativity (approximately 0 to 0.07), and path length (distance of 5 to median of 8)

This paragraph describes main results about male-bias in assorted networks with assortativity and heterogeneity only.

* In SLIRS simulations, no amount of sex-assortative mixing led to consistently target (i.e., sex-ratio observed in real data) male-bias (Fig 8).
* Without assortativity, SLIRS simulations indicate that heterogeneity in infectious period (IP) by sex can lead to target male-bias if male infectious period is twice as long as female infectious period () (Fig 9). Compared to heterogeneity in infectious periods (IP), heterogeneity in susceptibility (SUS) and transmission (TRA) rates by sex led to smaller, but larger than 1, prevalence ratios. As expected, higher ratios of heterogeneity () between male and female infection and transmission led to more discrepancy in infection by sex.

This paragraph describes combined effects of assortativity and heterogeneity on male-bias.

* With assortativity and heterogeneity in infectious period by sex, SLIRS simulations indicate male-bias can match or even exceed target male-bias (Fig 9). With moderate(?) assortativity levels () and a heterogeneity in infectious period (), target male-bias was reached in SLIRS simulations. In contrast, heterogeneity in susceptibility and transmission never consistently led to target levels of male-bias in SLIRS simulations at moderate assortativity levels (at , median male-bias was 1.7 when males were two times more susceptible than females).

This paragraph gives sensitivity of male-bias results to model structure.

* Similar to SLIRS simulations, assortativity alone did not lead to male-bias across any model structure (SIR, SLIR, and SIRS) and infectious period consistently led to more male-bias than susceptibility or transmissibility (Fig. 9). Models without reversion to susceptibility (SIR and SLIR) indicated target male-bias could be reached in more scenarios (e.g., in SLIR simulations, target male-bias was reached when or on networks with ).

Epidemic dynamics

* + The baseline transmission rates assessed here () represented sub-critical (), near critical (), and super-critical () transmission rates according to analytical solutions for the SIR model and numerical simulations (Fig. 7).
  + In general, high assortativity () had a negative effect on the equilibrium number of infected individuals (SIRS, SLIRS simulations; Fig. 11). However, when baselines transmission was low (, assortativity had a negligible relationship with equilibrium number of infected individuals. The negative relationship between equilibrium infected and assortativity strengthened with higher baselines transmission.
  + Similar to equilibrium infected, high assortativity () had a negative effect on total outbreak size and this was strengthened in simulations with higher baseline transmission rates (SIR, SLIR simulations; Fig. 12). In contrast with equilibrium infected, when baseline transmission was low (, assortativity increased total outbreak size. This was more pronounced in SIR simulations than SLIR simulations.
  + At the baseline transmission rates assessed here, assortativity had negligible (or slightly negative) effects on epidemic duration (SIR, SLIR; Fig. 10).
  + The presence of heterogeneity in infection and transmission at the individual-level had few consequences for equilibrium prevalence in general (Fig. 13).
  + Prevalence of latent infection target was not reached by any parameter combination (Fig. 14) for SLIRS simulations.

**Discussion outline:**

* Heterogeneity in infection by sex can consistently lead to male:female case ratios ­­­­­­­observed in real-world data.
* Assortativity cannot be a sole driver of male-bias but can contribute to amplifying the effects of heterogeneity in infection on male-bias.
* Heterogeneity in the infectious period led to more male-bias than differences in susceptibility or transmissibility by sex.
* The effects of assortativity on epidemic dynamics are sensitive to pathogen transmission rates. Pathogens with lower transmission can in some ways be boosted by spreading on highly assorted networks whereas pathogens with higher transmission are stymied by assorted networks.

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| **Problem** | **Response** |
| TB models make too many simplifying assumptions, especially the structure of the latent class and lack of age-structure, to accurately make inferences about biological mechanisms. | Our main results (about the relative effects of assortativity and heterogeneity in infection by sex) were consistent across model structures and transmission rates suggesting some generalizability. Overall, we believe these results suggest relative, rather than absolute, effect sizes of the different drivers of male-bias. |
| To inject assortativity into synthetic networks, edge re-wiring was performed. Unfortunately, this algorithm disrupted some network structural statistics and could slightly affect results about population-level epidemic dynamics, especially for high levels of assortativity. | Our results are in general agreement with Sah et al. (2017) which used a network generator (Sah et a. 2014) that maintained null network properties in modular networks. Specifically, when SIR diseases are considered, they (and others using a semi-analytical approach to this problem, see Nadini et al. 2018) find assortativity to decrease epidemic size in assorted networks. |
| There are few studies that calculate assortativity by sex (or report both respondent and contact sex in social mixing surveys) making it difficult to know the range of assortativity across human populations. | In Uganda, previous work estimated the sex-assortativity coefficient was 0.26 (which amounted to 65% of edges within-sex). A similar proportion of within-sex contacts was found in South Africa (62%). In general, we don’t expect sex-assortativity to be much higher than these studies but in regions with fewer differences in gender roles sex-assortativity could be lower. This is an area for future human social network research. |
| There is no evidence that heterogeneities in individual-level infection dynamics exist to the magnitudes set in this analysis | Susceptibility and transmissibility are unlikely to vary to degrees tested here between men and women. However, there is mounting epidemiological and immunological evidence for a period of ‘subclinical’ TB infection which we know regrettably little about. Our results point to infectious period as the most important of the transmission and infection variables at driving heterogeneity by sex and may reflect a higher propensity of subclinical infection in men than women, an important area for future research. |
| Model parameterization is very arbitrary. Why these transmission rates, recovery parameters, etc. | --- |

**Conclusions:** This study tested the potential for social mixing patterns and heterogeneity in infection by sex to drive sex-bias in TB, a pattern observed across human populations. We conclude that heterogeneity in infection, especially differing lengths of infectious periods, is more important relative to social mixing patterns but mixing patterns may amplify the effects of infection heterogeneities on male-bias. An important question related to these findings is whether the nature of sub-clinical or incipient TB differs in men and women and whether these differences are large enough to explain male-bias in TB. If found to be the case, these findings have applications for improving TB transmission tree reconstruction methods and case-finding.