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

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1. Summary

Globally, Tuberculosis disease (TB) is more common among males than females. Recent research proposes that differences in preferential social mixing by sex, or sex-assortativity, can alter infection patterns in TB. We conducted a simulation study to see whether sex-assorted mixing patterns can explain the global ratio of male:female TB cases and what factors might cause sex-disparities in infectious diseases to be sensitive to assortative mixing. Simulations showed sex-assortativity alone cannot cause sex-bias in TB. However, we find an effect of interaction between assortativity and sex-traits that suggests a role for behaviour to influence sex-specific epidemiology of infectious diseases. In our study, the role of sex-assortativity was especially apparent for slower spreading infectious diseases, like TB. We also examined how assortativity and sex-traits affect the final outbreak size and other epidemic dynamics. These results are important for understanding when sex-assortativity, a common feature across human populations, can change epidemiological patterns.

2. Introduction

Tuberculosis (TB) is now the leading cause of death due to infectious diseases globally, and notification data show that, on average, 1.8 male cases are reported for every female case (1). This pattern is strikingly consistent across all regions of the world with male:female ratios below 1 being extremely rare (2). Male-bias is also seen in adults of all ages but does not seem to apply to children (3). Differences in access to healthcare are not associated with this pattern as male-bias is observed in surveys using active case-finding (4,5). Moreover, male-bias is observed in developing and developed countries alike (2), further reducing the likelihood that male-bias is primarily driven by differences in access to healthcare since access to healthcare should be more equal in higher income countries. In fact, TB is not unique in being male-biased (among adults, 9 out of 11 infectious diseases were found to be male-biased (3). Understanding why sex-bias arises, in both TB and other infectious diseases, has widespread implications for basic research on sex-differences in disease and treatments (6), public health (7), and more realistic models and predictions of disease burden.

What causes male-bias in infectious diseases, and in TB, specifically? Proposed mechanisms are often categorized into "biological" or "social" (3,7). Hypothesized biological mechanisms for male-bias in TB are primarily related to a suspected higher male susceptibility to infection. For instance, female cells have two X chromosomes, which encode genes involved with both the innate and adaptive immune system and are thought to reduce susceptibility of females to a number of pathogens (Schurz et al. 2019). In addition, the female hormone estradiol enhances, while testosterone downregulates, macrophage activation which is an important pathway for initiating the innate immune response and consequently detecting M. tuberculosis

(reviewed in (8)). Another common explanation for increased male susceptibility to TB is smoking, which is more common among men (9) and can lead to damaged lung tissue (reviewed in (10)). Indeed at the country-level, adult smoking rates explain up to one-third of variation in male-bias (11). Other than susceptibility, there are additional, lesser studied biological mechanisms that could plausibly lead to male-bias. For instance, males are more likely to spread infection to their contacts than females (12,13), indicating higher male transmissibility. Finally, the length of time from disease to treatment can vary by sex, with males generally delaying care for longer period than females (14) suggesting males are infectious in the community for a longer period. Plausibly, therefore, these different sex-traits -- susceptibility, transmissibility, and infectious period -- could lead to male-bias in TB.

Gender-roles and preferences in social contacts may also cause males and females to have different exposure patterns (12,15,16). For example, one study found adult males travelled outside their village 75% more often than females and more than one-quarter of females identified as housewives, although there was no difference in the total number of contacts by sex (17). This suggests if social networks play a role in male-bias, it's not the number of social contacts but the pattern of social contacts that matters for transmission. Assortative mixing by sex is a common phenomenon across many cultures and because males are a higher incident demographic group than females, this social network structure may be important for understanding the basis for male-bias of TB (12,18). 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.

Infectious disease transmission models can help sort out the importance of various biological and social factors on sex-bias in infection. In this study, we use mathematical models of disease spread on social networks to examine the relative differences in sex-traits and preferential mixing by sex (i.e., assortativity), independently and in combination, required to give rise to observed levels of male-bias as seen in TB. We were also interested in whether the unique life history of human TB, with its long and variable latent period and endemic levels of infection in some regions, mediates the effects of sex-traits and assortative mixing on male-bias. To investigate these questions, we conducted a comparative simulation study of multiple transmission patterns (SIR, SLIR, SIRS, and SLIRS) spreading on contact networks that varied from random to extremely sex-assortative. Sex-traits investigated were sex-specific susceptibility, transmissibility, and infectious period.

3. Materials and Methods

General approach
We modelled the effects sex-assortativity (r, defined below) and sex-traits on male-bias. The sex-traits we considered were susceptibility, transmissibility, and infectious period. Susceptibility was defined as the rate of becoming infected given contact with an infected neighbour in the network. Transmissibility was the rate of infecting a susceptible neighbour in the network. Infectious period was defined as the period of time spent in the infected class before recovering. We quantified male-bias as the number of infected males divided by the number of infected females.

Network simulation
In simulated social networks, nodes represent individuals and edges between them represent repeated interactions between nodes on which infection can spread. To measure assortativity of simulated networks, we used Newman's discrete assortativity coefficient (19), $r = \frac{TrE - \|E^2\|}{1 - \|E^2\|}$, where E is the matrix with entries describing the fraction of edges of each sex. TrE is the fraction of edges that are within-sex. $\|E^2\|$ is the fraction of edges that would be within-sex if the edges were random.

To simulate social networks with varying levels of sex-assortativity, we used an algorithm presented in (20). The Sah algorithm is designed to simulate assorted networks that maintain network structures which alter epidemic dynamics including average clustering, path length, and degree assortativity (Badham and Stocker 2010). We simulated Sah networks with geometric degree distributions because other degree distributions (e.g., Poisson and power-law) often did not converge with two modules (i.e. sexes) which was the focus of this study. To determine whether networks with other degree distributions affected results, we conducted sensitivity analyses using networks generated with a simple rewiring scheme whereby we rewired between-sex edges of small-world and scale-free networks until desired levels of assortativity were reached and made sure the resulting networks were simple (i.e., no multiple edges or self-loops) and connected (i.e., only one component). Additional details on the rewiring algorithm are given in the Supplement. We chose these networks because they represent realistic human interaction networks (21). All networks were initialized with

1000 nodes (500 male, 500 female) and had a final mean degree of 10. We established how the rewiring algorithm affected network structural characteristics as we increased sex-assortativity, and compared changes to the Sah algorithm. We simulated 250 replicates of each network type and assortativity value.

Disease model
To study disease processes affecting sex-bias in TB, we varied parameters within a Susceptible-Latent-Infectious-Recovered-Susceptible (SLIRS) model framework corresponding to different assumptions about disease transmission (Table 1). For example, to incorporate latent tuberculosis infections, we turned on/off latent infection by changing the σ parameter ($\sigma \ll \infty$ leads to a SLIR model whereas $\sigma \to \infty$ leads to a SIR model). Similarly, to represent endemic levels of infection where "new" susceptibles reenter contact networks over longer time periods, we varied the ϕ parameter ($\phi \to 0$ leads to a SIR model whereas $\phi > 0$ leads to a SIRS model). Finally, to understand how overall pathogen transmissibility and corresponding R_0 affect results, we varied the overall τ. In SIR models, the analytical solution for the epidemic threshold (i.e., when $R_0 = 1$) is given by $\frac{\tau<K>}{\gamma<K^2-K>} > 1$ where K is the set of all node degree values in a network, K^2 is the set of all node degree values squared, and brackets indicate the mean of values in the set. Reproductive estimates for TB range from 0.24 to 4.3 (22). In simulations, varied values of R_0 from 0.5 to 3.5. We confirmed the epidemic threshold numerically (Figure S1). Thus, sensitivity analyses investigate different pathogen life histories and transmission rates.

Table 1. Transitions and parameter values for disease model.

Transition	Definition	Parameter	Average values
$S \to L$	Transmission rate	τ	$0.04, 0.075, 0.1$
$L \to I$	Incubation rate	σ	$0.1, \infty$
$I \to R$	Recovery rate	γ	0.5
$R \to S$	Reversion rate	ϕ	$1 \cdot 10^{-5}, 0.1$

To study how sex-bias could be generated though differences in male and female sex traits we varied the strength (α) of each sex-trait . For susceptibility, we multiplied male and female transmission rates, τ_m and τ_f, depending on the sex of the *target* node in the S-I edge pair. Specifically, for the male:female susceptibility ratio, α_s, we solved the following equations

$$\tau_m = \alpha_s \tau_f$$
$$\frac{\tau_m + \tau_f}{2} = \tau,$$

which hold the overall susceptibility rate constant and results in the following solution:

$$\tau_m = \frac{2\alpha_s\tau}{1+\alpha_s} \quad \tau_f = \frac{2\tau}{1+\alpha_s} .$$

Thus, when $\alpha_s = 1$, $\tau_m = \tau_f = \tau$ and when $\alpha_s > 1$, the average susceptibility is still τ. Sex differences in transmissibility were modeled in a similar way, adjusting the rates depending on the sex of the *source* node in the S-I edge pair. Sex differences in the duration of the infectious period (inverse of the recovery rate) were modeled by changing the male and female γ parameters. Specifically, we wanted the average infectious period to remain $1/\gamma$ so we solved the same equations, except holding the average infectious period ($1/\gamma$) rather than the average recovery rate (γ) constant.

We implemented the model as a continuous-time Markovian model using the Epidemics on Networks (23) and Networkx packages (https://networkx. github.io/) in Python (Version 2.7.17).

Analysis
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 infections in the SIRS and SLIRS model structures. For the SIR and SLIR models, simulations were run until there were no infected individuals left. For the SIRS and SLIRS models, simulations were run until there were no infected individuals left or for 250 timesteps (whichever came first). For the SIRS and SLIRS models, we performed preliminary analyses to determine when simulations reached endemic levels of infection and parameters required to lead to 25% of the population having latent infection at equilibrium (24).

To compare the effects of assortativity and heterogeneity in individual-level infection on epidemic dynamics, we calculated the final size, epidemic duration, equilibrium latent and infected prevalence for each simulation. From the prevalence of latent infection at endemic equilibrium in the SLIRS model given different parameter

combinations, we assessed parameter ranges for the transmission rate that approximate TB. In 2017, 1.7 billion people (23% of the world's population) were estimated to have latent TB infection (1)

We used R Version 4.0.0 for analyses and visualizations. All Python and R scripts are available at github.com/drakelab/miller-tb-assortativity.

4. Results

In simulated networks, the proportion of within-sex contact increased with r, from 45% when r=0 to 77% when r=0.6 (Figure 1). Results from a meta-analysis of the proportion of within-sex mixing among adults (18), correspond to values of sex-assortativity from r=0.2 to 0.3, which also aligns with an independent estimate of sex-assortativity for a social network in Uganda (Miller et al. 2020).

Effects of sex-traits and assortativity on male-bias
In simulations, sex-assortativity did not lead to male-bias. This result was not sensitive to model type (SIR, SLIR, SIRS, SLIRS) or network type (Sah networks, rewired small-world, rewired scale-free) (Figure 2, Figure 3, Figure S2, Figure S3).
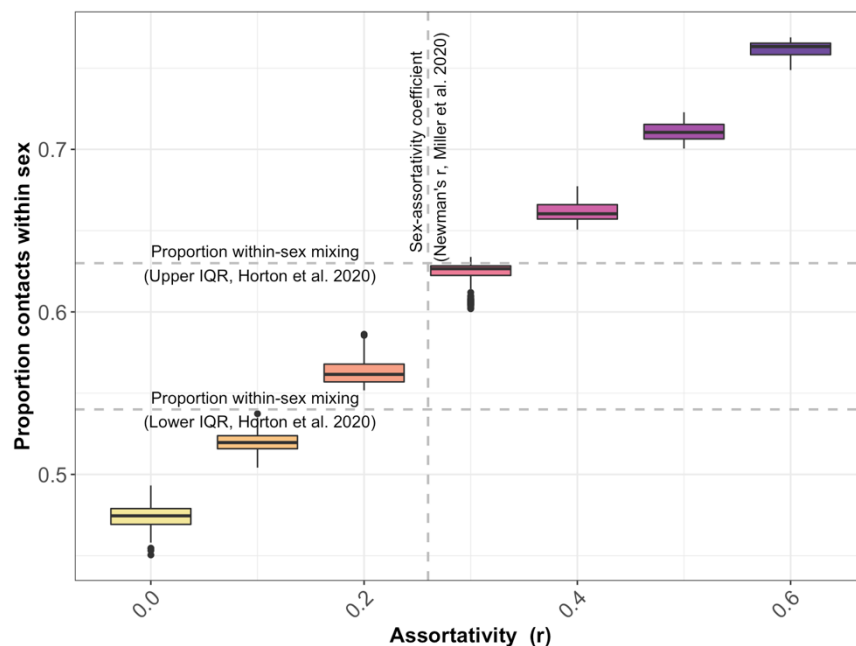

Figure 1. The proportion of contacts within-sex tracks with Newman's r. For context, the range of proportional within-sex mixing from a meta-analysis by Horton et al. (2020) is shown in horizontal grey-dashed lines and the sex-assortativity coefficient from a social network in Uganda in a horizontal dashed line. Boxplots show calculated proportional within-sex mixing from 250 simulated networks at each assortativity level.

Combined with sex-traits (susceptibility, transmissibility and infectious period), however, assortativity increased male-bias (Figure 2). The first sex-trait that we investigated, increased male susceptibility (SUS), led to male-bias in the absence of sex-assortativity but epidemics on assorted networks had higher male-bias than networks without sex-assortativity (Figure 2). This result was not sensitive to inclusion of a latent class (Figure S3). The interactive effect of sex-assortativity and sex-traits on male-bias grew with the strength of male:female susceptibility. This was observed across all model types: without sex-assortativity median values of male-bias are below 1.8 while median values of male-bias with sex-assortativity can exceed 1.8. The amplification effect of sex-assortativity on male-bias was not as pronounced in rewired scale-free networks as rewired small-world networks or Sah networks (Figure S2).

The interaction of assortativity and sex-traits on male-bias was especially notable in the case of increased male transmissibility (TRA). Without sex-assortativity, even when males had more than three-fold higher transmissibility, male infections were no more likely than female infections (Figure 2, Figure S2). Overall, however, higher male transmissibility rarely resulted in ratios of male-bias observed in global TB data.
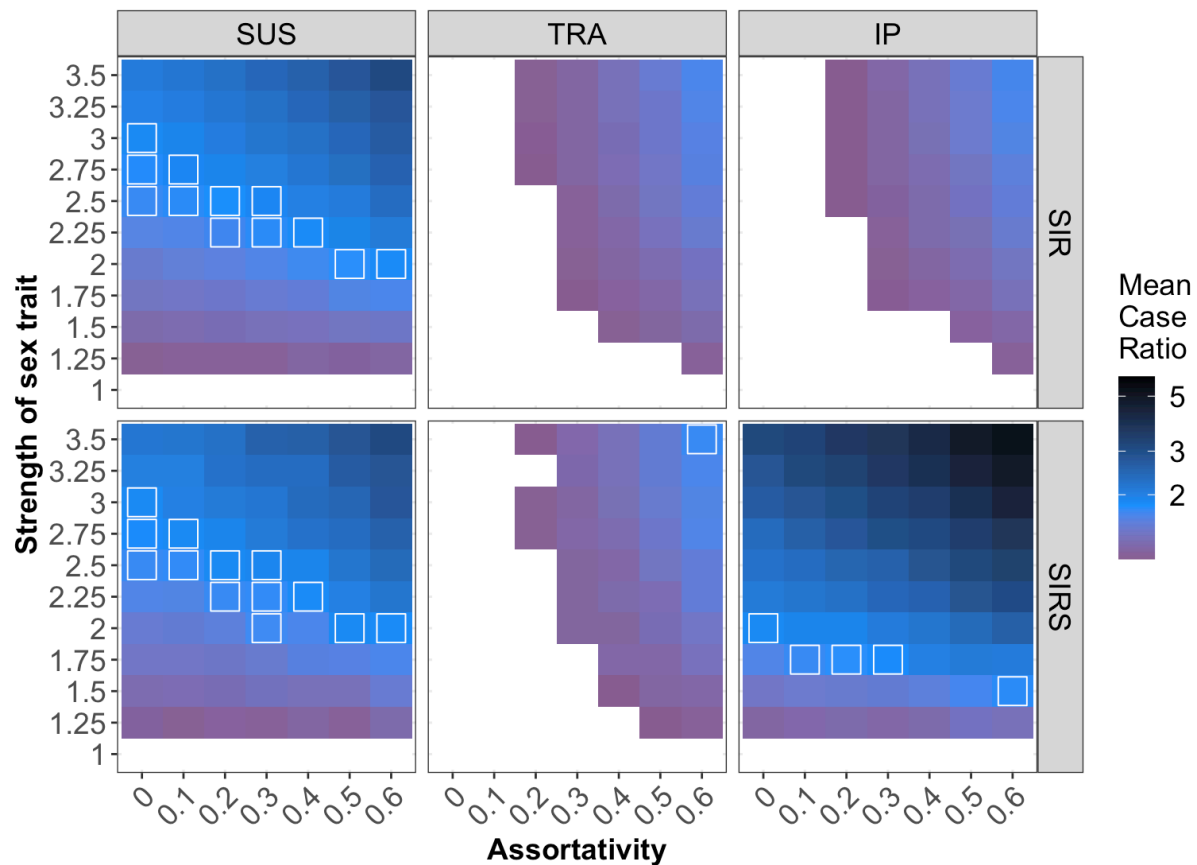
Figure 2. M:F case ratio is influenced by sex-assortativity and sex-traits (columns). Sex-traits are susceptibility (SUS), transmissibility (TRA), and infectious period (IP). M:F case ratio is measured as the ratio of male to female recoveries (SIR) or infections at equilibrium (SIRS). Only parameter 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. Sex-traits are incorporated by holding respective overall parameter rates constant but increasing the male parameter by the value on the y-axis relative to the female trait. Figure generated with 250 simulations of epidemics on Sah networks with $\tau = 0.04, R_0 \approx 1.5$.

Longer male infectious periods (IP), similar to higher male transmissibility, did not lead to male-bias in SIR and SLIR epidemics unless taking place on sex-assorted networks (Figure 2, Figure S3). In the parameter ranges investigated here, median values of male-bias for simulations of longer male infectious periods in SIR and SLIR models were all below 1.8. However, when recovered individuals can re-enter the susceptible population (i.e., SIRS and SLIRS models), longer male infectious periods can result in male-bias and there is a slight increase in male-bias on assorted networks. In SIRS and SLIRS models, male-bias due to longer male infectious periods was possible. These results were not sensitive to network type (Figure S2).

Transmission rate increased the effect of assortativity on male-bias (Figure 3). For a slow spreading pathogen ($\tau = 0.04, R_0 \approx 1.5$) and male susceptibility twice that of female susceptibility, male-bias increased from a median of 1.48 without assortative mixing to 1.85 with strong assortativity (r=0.6) indicating a 25% increase in male-bias with assortative mixing. For a faster spreading pathogen ($\tau = 0.1, R_0 \approx 3.5$) with the same level of higher male susceptibility, male-bias only increased from a median of 1.28 to 1.34 indicating a 5% increase in male-bias with assortative mixing. Similar relationships were observed for the other sex-traits, transmissibility and infection period.
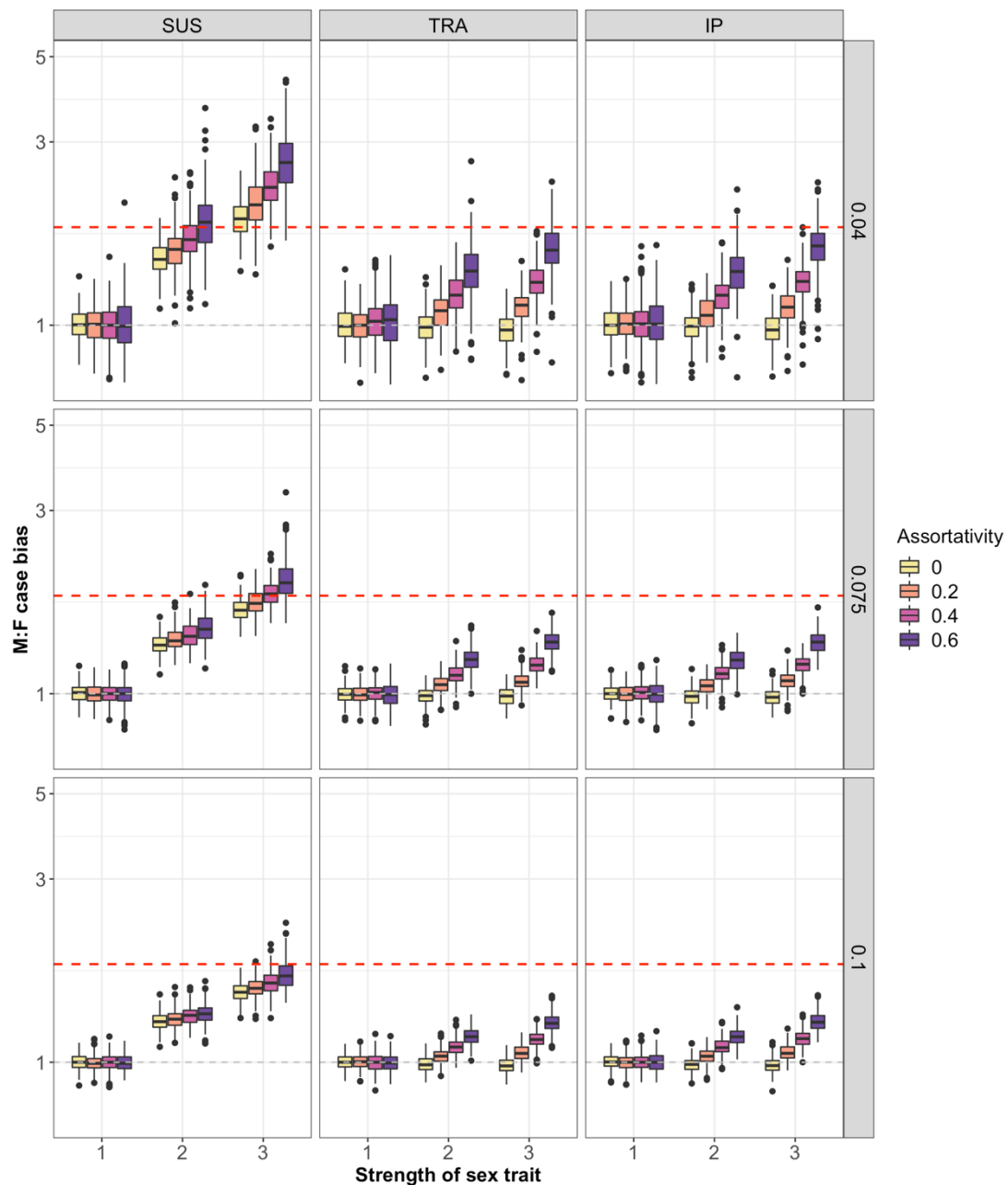
Figure 3. Sex-assortativity increases M:F case bias more for pathogens with lower overall infection rates compared with higher overall infection rates (rows). The M:F case bias and sex-traits, are defined in the same way as in Figure 1. To improve figure clarity, only 3 levels of sex-trait strength are shown here. Figure generated with 250 SLIR simulations of epidemics on Sah networks.

Effects of sex-traits and assortativity on epidemic outcomes

In general, on Sah contact networks epidemic dynamics were not affected by sex-assortativity or sex-traits (infectious periods, susceptibility, and transmissibility) including the peak size, final size, and duration for SIR or SLIR epidemics (Figure S4). Higher male susceptibility slightly reduced the final size of epidemics for faster spreading pathogens but the effect was small (Figure 4). In contrast to results on Sah networks, assortativity was associated with changes in peak size, final size, and duration on rewired network (Figure 5). We note, however, that while networks generated with the Sah algorithm had stable network structures as sex-assortativity increased, rewired networks did not (Figure S5). As assortativity increased from r=0 to r=0.6, clustering increased by approximately 10% in scale-free networks and decreased by approximately 60% in small-world networks. With increasing assortativity, average network path length increased by about 10% in scale-free networks and decreased by approximately 25% in small-world networks. In both small-world and scale-free networks, degree-assortativity increased as sex-assortativity increased.
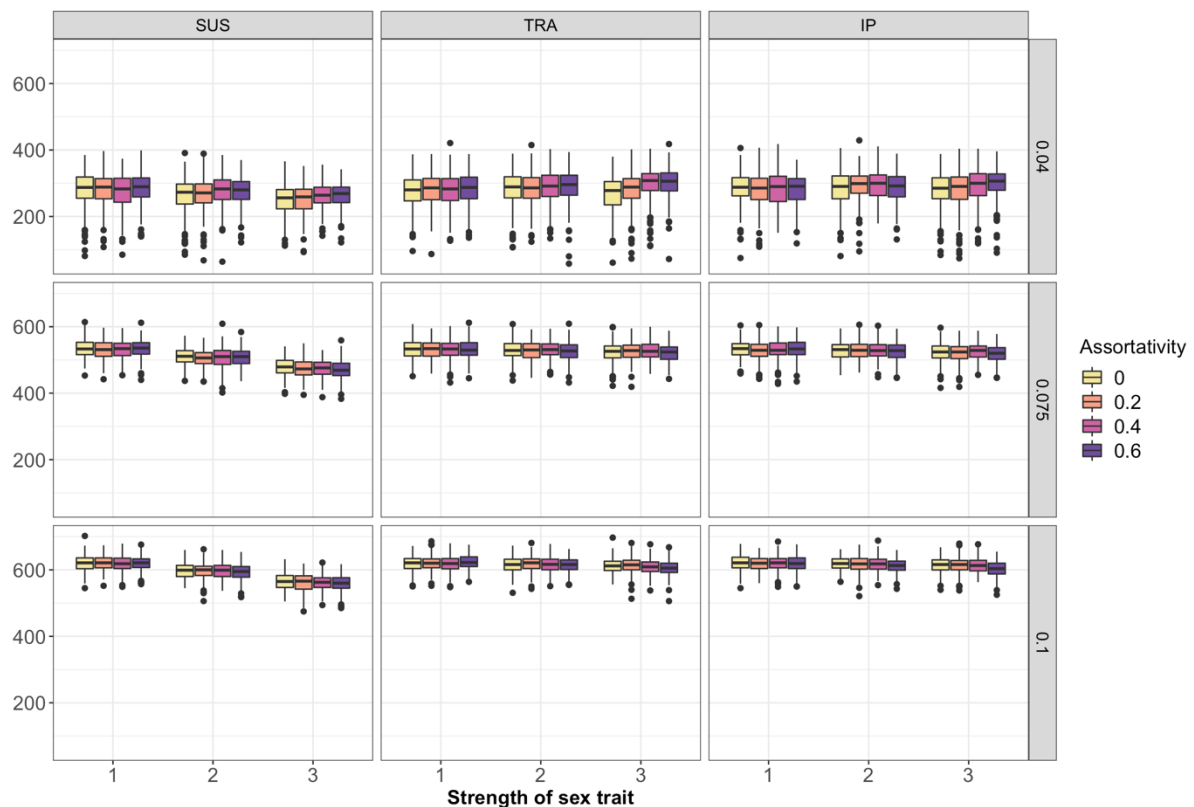
Figure 4. Sex-assortativity and sex-traits (columns) generally have negligible effects on the final epidemic size compared with the effect of transmission rate (rows). To improve figure clarity, only 3 levels of sex-trait strength are shown here. Figure generated with 250 SLIR simulations of epidemics with varying transmission rates on Sah networks.

5. Discussion

Social mixing patterns can alter transmission patterns of infectious diseases (25-27). We conducted a comparative simulation study to see whether sex-assorted mixing patterns can explain the global ratio of male:female TB cases. Simulations showed sex-assortativity alone does not cause sex-bias in TB. However, an interaction between assortativity and sex-traits does affect the ratio of male to female infections suggesting a role for behaviour to influence sex-specific epidemiology of infectious diseases. The role of sex-assortativity was especially apparent for slower spreading infectious diseases, like TB (28). We also examined the role of sex-assortativity and sex-traits on the final outbreak size and other overall epidemic dynamics.

Our main result showed that subtle but widespread patterns in sex assortativity may shape sex-specific epidemiological patterns. Approximately 55-65% of human social interactions occur within-sex (12,18, Miller et al., unpublished manuscript), which we showed corresponds to assortativity coefficients of 0.2 to 0.4. Within this range, our simulations suggested that assortative mixing can change sex-specific epidemiological patterns when there are underlying heterogeneities in sex-traits, especially for slower spreading infectious diseases. For example, SIR simulations showed longer male infectious periods and higher male transmissibility only produced male-biased infection patterns in the presence of moderate (greater than 0.3) values of sex-assortativity. On the other hand, higher male susceptibility could lead to male-bias in infection alone. However, male-bias was higher in outbreaks on sex-assorted networks compared with non-assorted networks. Our finding that slower spreading infectious diseases were more sensitive to differences in assortativity is similar to previous results, which suggested slower spreading pathogens experience structural trapping (i.e., stochastic extinction) while faster spreading pathogens experience structural delay (i.e., spread between subgroups is merely delayed) (29). Overall these results suggest that sex-assortativity can increase the effects of infection differences between males and females on sex-disparities in infectious diseases, especially for slow spreading pathogens, like TB.

Our conclusion that sex-assortativity can increase sex disparities in TB hinges on there being relatively large differences in sex-traits, defined here as susceptibility to infection, length of the infectious period, and rate of transmissibility to contacts. 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) but the relative difference in specific rates is a complex question. The first of the three traits investigated here, higher male susceptibility, has been studied experimentally. In one study, castration reduced infection following exposure by half in male mice but doubled infection following exposure in female mice (reviewed in (15)). Susceptibility is also linked to male-

dominated risk factors such as smoking (31) and alcohol use (32). However, some household studies have found no difference in incidence of TB within households of infectious cases (33). These converging lines of evidence make it difficult to ascertain the overall difference in male:female susceptibility, but it is likely a crucial determinant of male bias in TB.

We also explored the effects of higher male transmissibility and longer male infectious periods, although there is less evidence for these mechanisms than for differences in susceptibility. 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). Additionally, household contacts of male cases had a higher prevalence of latent infection than female cases (ORs of 4.05 in univariate analyses; 7.62 in multivariate analyses) (13). However, our simulations showed no evidence that transmissibility can generate sex-disparities, unless the relative difference in male and female transmissibility was large, similar to modelling results in (34). The last trait, which assumes there could be variation of the infectious period of TB, is a developing area of research. Males are more likely to delay care and diagnosis (14), possibly resulting in longer periods of infectiousness in the community. Our simulations indicated for sex differences in the infectious period to cause sex disparities in infection, the difference in infectious period would have to be large and sex assortative mixing would be required. In reality, there are still many unknowns about the nature of the infectious period in TB cases generally (35,36) and whether and how the infectious period could vary between sexes is an open area of work. In addition, a combination of these traits may culminate to produce the consistently male-biased case notification data we see for TB. Future experimental and epidemiological studies are needed to better quantify the differences immunity and infection rates by sex because they all could have different implications for control programs.

Overall epidemic dynamics, such as final outbreak size, peak timing, and outbreak duration, can also be effected by assortativity (also known as modularity, or social grouping) in some situations (29,37,38). In our simulations, however, with only two groups (male and female) and moderate assortativity, there are few differences in overall dynamics. Previous studies that have found assortativity to alter the final outbreak size have mostly examined the situation where there are many groups with high levels of assortativity (0.8-0.95) (29,37). Differences in the direction of change attributed to assortativity can be explained by different assumptions about immunity (38) and also whether high levels of assortativity in realistic contact networks are associated with increased network clustering (37) which has the effect of lower overall outbreak size (39). We find similar results in our simulations. For example, our rewired scale-free networks increased in clustering with increased assortativity and found assortativity to decrease final size. Thus, our simulations further aid in understanding the situations when assortativity can affect important outcomes of outbreaks.

While our simulations tested multiple model assumptions, and our results were not sensitive to parameters chosen, these simplistic models do not fully capture the complexities of TB, especially in light of recent advances in our understanding of the spectrum of infection and disease (35). In addition, our social contact networks omit age-specific infection rates and age-specific mixing patterns, which are important for accurately estimating TB burden in a population (27). Because the aim of this study was to test a general phenomenon, our models were not parameterized for specific populations. Epidemiologically-relevant demographic variables, such as the reproductive rate, vary across populations (22), which may influence the applicability of these results to specific populations. The goal of our modelling study was to offer qualitative insight into whether assortativity may play a role in causing sex-disparities in TB and other possible pathogen scenarios that might be affected by sex assorted mixing.

6. Conclusion

These results provide insight into how behaviour can amplify the consequences of evolutionary trade-offs between sex and immunity to infection. Although we focused on TB, many infectious diseases are male-biased (3) and most populations have social mixing patterns marked by sex-assortativity (18). We conclude that heterogeneity in sex rates, especially differing susceptibility, is more important to sex-disparity in infectious diseases than sex-assortativity, but mixing patterns can amplify the effects of sex-traits in some cases. For TB, important questions arise about whether differences in susceptibility and other sex-traits, are similar to levels analyzed here or if there are remaining factors driving sex-disparities in TB. For practical purposes, results from this study shed light on when it could be inappropriate or misleading to extrapolate infection risk or rates across sexes for different models.

Data Accessibility

The code to reproduce results in this article are archived in the github repository https://github.com/DrakeLab/miller-tb-assortativity.

Competing Interests

We declare no competing interests.

Authors' Contributions

P.M. performed the simulations and wrote the first draft of the manuscript. P.M., C.W., and J.D. jointly interpreted the results and edited the paper.

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