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

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ABSTRACT

Globally, Tuberculosis disease (TB) is more common among men than women. Recent research proposes that differences in social mixing by sex 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 social mixing by sex alone cannot cause sex-bias in TB. However, we find an effect of interaction between assortativity and sex-traits that suggests a role for behavior 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 overall epidemic dynamics. These results are important for understanding when preferential social mixing by sex, a common feature across human populations, can change epidemiological patterns.

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 (World Health Organization 2018). This pattern is strikingly consistent across all regions of the world with male:female ratios below 1 being extremely rare (Neyrolles and Quintana-Murci 2009). Male-bias is also seen in adults of all ages but does not seem to apply to children (Guerra-Silveira and Abad-Franch 2013). Differences in access to healthcare are not associated with this pattern as male-bias is observed in surveys using active case-finding (Salim et al. 2004; Borgdorff et al. 2000). Moreover, male-bias is observed in developing and developed countries alike (Neyrolles and Quintana-Murci 2009), 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 (Guerra-Silveira and Abad-Franch 2013). 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 (Clayton 2016), public health (World Health Organization 2007), 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” (World Health Organization 2007; Guerra-Silveira and Abad-Franch 2013). 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 (Schurz et al. 2019)). Another common explanation for increased male susceptibility to TB is smoking, which is more common among men (Islami, Torre, and Jemal 2015) and can lead to damaged lung tissues (reviewed in (Centers for Disease Control and Prevention (US), National Center for Chronic Disease Prevention and Health Promotion (US), Office on Smoking and Health (US) 2010)). Indeed at the country-level, adult smoking rates explain up to one-third of variation in male-bias (Watkins and Plant 2006). 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 (Dodd:2016gw; Hector et al. 2017), also potentially causing higher infectiousness of men. Finally, the rate of progression from infection to disease can vary by sex and age, with reproductive-age females generally progressing from latent to active infection faster than males (Holmes, Hausler, and Nunn 1998) while being diagnosed at the same rate as males (Salim et al. 2004), suggesting a longer period from initial infection to diagnosis for males. Therefore, these different sex-traits -- susceptibility, transmissibility, and infectious period -- could lead to male-bias in TB.

On the social side, gender-roles and preferences in social contacts may cause males and females to have different exposure patterns (Nhamoyebonde and Leslie 2014; Dodd et al. 2016; Horton et al. 2016). For example, one study found adult males travelled outside their village 75% more often than women and more than one-quarter of women identified as housewives, although there was no difference in the total number of contacts by sex (le Polain de Waroux et al. 2018). 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 marked 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 (Dodd et al. 2016; Horton et al. 2020). 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 modeling 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.

METHODS

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 (Newman 2003), **,** where is the matrix with entries describing the fraction of edges of each sex. is the fraction of edges that are within-sex. 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 (Sah et al. 2014). 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 (Anderson:1991ta; 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. For sensitivity analyses, we developed a simple rewiring scheme whereby we rewired between-sex edges of small-world and scale-free networks until desired levels of assortativity were reached (within 0.05) 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(Eubank et al. 2004). 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.

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, we turned on/off latent infection by changing the parameter. Similarly, to represent endemic levels of infection where “new” susceptibles reenter contact networks over longer time periods, we varied the parameter. Finally, to understand how overall pathogen transmissibility and corresponding affect results, we varied the overall τ. In SIR models, the analytical solution for the epidemic threshold (i.e., when is given by where K is the set of all node degree values in a network, 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 (Ma et al. 2018). In simulations, we varied values of from 0.5 to 3.5. We confirmed the epidemic threshold numerically (Figure R0). Thus, sensitivity analyses investigate different pathogen life histories and transmission rates.

**Table 1.** Transitions and parameter values for disease model.

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| **Transition** | **Parameters** | **Average values** |
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To study how sex-bias could be generated though differences in male and female sex traits we varied the ratio of male to female susceptibility, transmissibility, and infectious period (, , and ). For susceptibility, we changed the rates of and depending on the sex of the *target* node in the S-I edge pair. Specifically, for the male:female susceptibility ratio, we solved the following equations:

This results in susceptibility of male and female nodes to be:

So that when and when , the average susceptibility is still . 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 were modeled by changing the male and female parameters. Specifically, we wanted the average infectious period to remain so we solved the same types of equations, except holding the average infectious period () rather than the average recovery rate () constant.

We implemented the model as a continuous-time Markovian model using the Epidemics on Networks (Miller and TIng 2020) 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 (Houben and Dodd 2016).

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 (World Health Organization 2018)

We used R Version 4.xxx for analyses and visualizations. All Python and R scripts are available at github.com/drakelab/miller-tb-assortativity.

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 (Horton et al. 2020), 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).

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| **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. |

In the absence of sex-traits, sex-assortativity did not lead to male-bias in TB prevalence. This result was not sensitive to model type (SIR, SLIR, SIRS, SLIRS), overall transmission rate, or network type (Sah networks, rewired small-world, rewired scale-free) (Figure 2, Figure 3, Figure NET\_TYPE, Figure LATENT).

Combined with sex-traits, however, assortativity increased male-bias (Figure 2), especially for slower spreading pathogens relative to faster spreading pathogens (Figure 3). 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 NET\_TYPE). Overall, however, higher male transmissibility rarely resulted in ratios of male-bias observed in global TB data.

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| **Figure 2**. M:F case ratio is influenced by sex-assortativity and sex-traits. Sex-traits (vertical columns) are infectious period (IP), susceptibility (SUS), and transmissibility (TRA). M:F case bias 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 (white boxes show 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 x-axis relative to the female trait. Figure generated with 250 simulations of epidemics on Sah networks with |

Similarly, epidemics with longer male infectious periods (IP) did not lead to male-bias in SIR and SLIR epidemics unless taking place on sex-assorted networks (Figure 2, Figure LATENT). In contrast, longer male infectious periods can result in male-bias without assortativity in SIRS and SLIRS epidemics. 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. In SIRS and SLIRS models, male-bias due to longer male infectious periods was possible. These results were not sensitive to network type (Figure NET\_TYPE).

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| **Figure 3.** Sex-assortativity increases M:F case bias more for pathogens with lower overall infection rates compared with higher overall infection rates (horizontal facets). The M:F case bias, sex-traits, and relative male:female values of sex-traits are the same as in Figure 1. Figure generated with 250 SLIR simulations of epidemics on Sah networks |

The final sex-trait that we investigated, increased male susceptibility (SUS), led to male-bias in the absence of sex-assortativity across all model types but epidemics on assorted networks had higher male-bias than networks without sex-assortativity (Figure 2, Figure LATENT). 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 NET\_TYPE).

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| **Figure 4.** Sex-assortativity has negligible effects on peak size, final epidemic size, and epidemic duration. Sex-traits are the same as in Figure 1. Figure generated with 250 SLIR simulations of epidemics with and on Sah networks |

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| **Figure 5.** The effect of assortativity on the final size or equilibrium prevalence of SIR and SIRS epidemics depends on underlying network type. Results are shown for outbreaks with no differences in male and female sex-traits. Figure generated with 250 simulations of epidemics. |

In general, 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 on Sah networks (Figure 4). One notable exception was that higher male susceptibility reduced the final size of epidemics. As for rewired networks, assortativity was associated with changes in peak size, final size, and duration (Figure 5, Figure EPI\_STR). We note, however, that while networks generated with the Sah algorithm had stable network structures as sex-assortativity increased, rewired networks did not (Figure NET\_STR). 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.

DISCUSSION

Social mixing patterns can alter transmission patterns of infectious diseases (Mossong et al. 2008; Rohani, Zhong, and King 2010; Arregui et al. 2018). 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 social mixing by sex cannot cause sex-bias in TB alone. However, an interaction between assortativity and sex-traits on the ratio of male to female infections suggests a role for behavior to influence sex-specific epidemiology of infectious diseases. The role of sex-assortativity was especially apparent for slower spreading infectious diseases, like TB. We also examined the role of sex-assortativity and sex-traits on the final outbreak size and other overall epidemic dynamics.

Our simulations illustrated that subtle but widespread patterns in sex assortativity may shape sex-specific epidemiological patterns. Approximately 55-65% of human social interactions occur within-sex (Dodd et al. 2016; Horton et al. 2020)(Miller et al., 2020), corresponding 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) (Sah et al. 2017). Overall these results suggest that preferential social mixing by sex can increase the effects of immunity and 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 are real differences in immunity and infection for TB between males and females (Salim et al. 2004; Guerra-Silveira and Abad-Franch 2013; Nhamoyebonde and Leslie 2014; Rhines 2013) 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, though some household studies have found counterevidence (CITE DR WHALEN). In one study, castration reduced infection following exposure by half in male mice but doubled infection following exposure in female mice (reviewed in (Nhamoyebonde and Leslie 2014)). Susceptibility is also linked to male-dominated risk factors such as smoking (Bates et al. 2007) and alcohol use (Lönnroth et al. 2008). All these converging lines of evidence make it difficult to estimate the overall difference in male:female susceptibility, but it is likely a crucial factor in male:bias of 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, males were estimated to cause 1.3 to 1.8 times higher proportion of infections than females in South Africa and Zambia (Dodd et al. 2016). Additionally, male sex is a high risk factor (ORs of 4.05 in univariate analyses; 7.62 in multivariate analyses) for TST positivity in household contacts (Hector et al. 2017). 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 modeling results in (Perkins, Ferrari, and Hudson 2008). The last trait, which assumes there could be variation of the infectious period of TB, is a developing area of research. Prospective studies find progression rates to disease can vary by sex (and age), with reproductive age females generally progressing to disease faster than males (Holmes, Hausler, and Nunn 1998) which we speculated could have implications on the period of infectiousness in the community if following progression to active disease, females were then diagnosed at the same rate as males (Salim et al. 2004). 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 biology of TB (Xu et al. 2019) and 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 potential for each of these immunity and infection rates 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 (Salathé and Jones 2010; Sah et al. 2017; Nadini et al. 2018). 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) (Salathé and Jones 2010; Sah et al. 2017). Differences in the direction of change attributed to assortativity can be explained by different assumptions about immunity (Nadini et al. 2018) and also whether high levels of assortativity in realistic contact networks are associated with increased network clustering (Salathé and Jones 2010) which has the effect of lower overall outbreak size (Badham and Stocker 2010). 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 in the main text, these simplistic models do not fully capture the complexities of TB, especially with regard to the clinical spectrum of infection and disease. 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 (Arregui et al. 2018). Because the aim of this study was to test a general theory/phenomenon/pattern, our models were not parameterized for a specific population. Epidemiologically-relevant demographic variables, such as the reproductive rate, vary across populations (Ma et al. 2018), which may influence the applicability of these results to specific populations. The goal of our modeling 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.

These results provide insight into how behavior 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 (Guerra-Silveira and Abad-Franch 2013) and most populations have social mixing patterns marked by sex-assortativity (Horton et al. 2020). 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.

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