The effects of sex traits and assortative mixing on sex-bias in Tuberculosis:

A modelling study

**Authors:** PB Miller, CC Whalen, JM Drake

**Study narrative**: Infectious diseases often affect males and females differently. Reasons why include different social mixing patterns and sex-traits of males and females. We wanted to understand the potential impact of social mixing (assortativity) and sex-traits on the sex-bias in TB, which is male-biased. We wanted to learn this because it’s interesting to think about how social and biological factors combine at the individual-level to produce widespread differences in infection at the population-level. Also, the relative potentials for previous explanations for sex-bias have never been systematically assessed alongside each other in a model. Finally, understanding drivers of male-bias might inform treatment/vaccine research and public health control strategies. To determine the relative effects of mixing patterns and sex-traits, we conducted a comparative simulation study of pathogen scenarios spreading on networks that varied from random to extremely sex-assortative. Sex-traits investigated were sex-specific susceptibility, transmissibility, and infectious period. We found no evidence that assortativity by sex can drive male-bias in TB alone, even at extreme levels. Instead, sex-traits alone or combined with sex-assortativity can lead to realistic levels of male-bias observed globally. Overall epidemic dynamics were mostly unchanged by the presence of sex-traits.

**Introduction:** This paragraph sets the stage for male-bias in TB.

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 developed 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 how sex-bias happens, both in TB and other infectious diseases, has widespread applications including for basic research on sex-differences in disease and treatments 6, public health 7, and more realistic models and predictions of disease burden.

This paragraph reviews biological and social factors related to male-bias of infections, and TB specifically.

What causes male-bias in infectious diseases, and in TB, specifically? Typically, proposed mechanisms are categorized into “biological” or “social” 7 3. Biological differences between males and females exist at every biological scale. At the cellular level, female cells have two X chromosomes, which encode genes involved with both the innate and adaptive immune system and are thought to contribute to an overall more robust female immune response to a number of pathogens. 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). Affecting organ tissues, males have a higher tendency to smoke 9 which can damage lung tissue (reviewed in 10) and, in heavy smokers, is associated with increased Tuberculosis cases rates up to four-fold 11. On the social side, societal gender-roles and preferences in social contacts may lead men to have higher exposure rates due to work, travel, or higher preference of same-sex social contacts 12-14. Thus, social factors could lead men to have more exposure opportunities overall or cause men to preferentially contact men, which (due to biological factors listed above) could be at higher risk of infection themselves. Combined, these factors make “sex” a risk factor independent of other variables (varying from \_\_\_ to \_\_\_ in CITE MULTIVARIATE REGRESSION ANALYSES).

This paragraph discusses magnitude of the factors, and their unknown effect at population scale.

How different biological and social contact factors are between males and females and how much each contributes to male-bias at the population-level is less well-understood. At the country-level adult smoking rates explain up to one-third of variation in male-bias 15, and remaining variation is likely due to a number of sex-related infection and societal gender-related factors. Mice models indicate male mice are \_\_\_ more likely to develop disease than female mice (CITE). In an influenza study, men generate 25% more air particles than women during coughing (see supplement 16). Rate of progression from infection to disease can vary by sex and age, with females generally progressing faster than males (up to 30% faster), suggesting longer latent periods in men (reviewed in {Holmes:tz}). Exposure, measured by Tuberculin Skin Tests, was \_\_\_ higher in adult males compared with adult females but did not vary among children (CITE GUERRA). Also, men traveled \_\_\_ more often (CITE) and have \_\_\_ more male contacts than females in some high-burden populations (CITE Dodd, Miller et al. 2020). Whether any of these factors, 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.

This paragraph describes our 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, changed the effects of sex-traits and assortative mixing on male-bias. To investigate these questions, we conducted a comparative simulation study of multiple pathogen scenarios (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*

This paragraph describes networks and how we measure of assortativity in simulated networks.

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, **,** 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. Modularity, , is another common statistic to measure within-group mixing. In the context of two equal-sized groups (i.e., sexes) .

This paragraph describes the process of simulating assorted networks.

To simulate social networks with varying levels of sex-assortativity, we used two types of algorithms: a re-wiring algorithm and an algorithm presented in Sah et al. (2015). For the rewiring algorithm (details below), networks were initialized as small-world or scale-free networks because these networks resemble patterns of clustering and high-degree network hubs found in real-world social networks. Small world networks were initialized with \_\_\_ parameters and scale free networks were initialized with \_\_\_ parameters.

**Table 1.** Network rewiring algorithm.

1. Simulate a network
2. Randomly assign node sex
3. Rewire a proportion of edges occurring between-sex
4. Check that the network is still a single component, if not, reject rewiring and return to step 3
5. Check for multiple edges or self-edges, and randomly rewire those edges
6. Continue process until the desired level of assortativity was reached within a small range of error

This paragraph describes the process of simulating assorted networks with the Sah algorithm.

The Sah (2014) algorithm is designed to simulate networks which maintain average clustering, path length, and degree assortativity as assortativity is increased. However, the method is limited to modeling simpler networks when there is high modularity and few groups due to the requirements of the algorithm. For this analysis, we initialized Sah networks with a geometric degree distribution and a mean degree of 10. All networks were initialized with 1000 nodes and had a final mean degree of 10. For each network, we set 500 male and 500 female nodes. To establish how the algorithms affected network structural characteristics as we increased sex-assortativity, we compared network clustering, degree assortativity, and path length across sex-assortativity levels.

*Disease model*

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

To study disease processes affecting sex-bias in TB, we varied parameters within a Susceptible-Latent-Infectious-Recovered-Susceptible (SLIRS) model corresponding to different assumptions about disease transmission. 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 affects results, we varied the overall τ. In these ways, the disease model can represent SIR, SLIR, SIRS, and SLIRS structures.

**Table 2.** Transitions and parameter values for disease model.

|  |  |  |
| --- | --- | --- |
| **Transition** | **Parameters** | **Average values** |
|  |  |  |
|  |  |  |
|  |  |  |
|  |  |  |

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

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 set of 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 the exact same way; except we changed 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 package (CITE) in Python (Version 2.7.17).

*Analysis*

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

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. 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 250 time steps (whichever came first). For the SIRS, SLIRS models, we performed preliminary analyses to determine when simulations reached endemic levels of infection.

This paragraph explains how we compared epidemic dynamics.

To compare 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. Finally, we measured the prevalence of latent infection at endemic equilibrium in the SLIRS model to understand how model output relates to real data. In 2017, 1.7 billion people (23% of the world’s population) were estimated to have latent TB infection (2018 WHO TB Report).

All computer code and instructions to reproduce results are available at github.com/drakelab/miller-tb-assortativity.

**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 ).

This paragraph describes characteristics of epidemics given parameters tested here.

* 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:**

This paragraph highlights the main findings about assortativity and heterogeneity in infection.

* 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 infection by sex can consistently lead to male:female case ratios ­­­­­­­observed in real-world data.
  + Heterogeneity in the infectious period led to more male-bias than differences in susceptibility or transmissibility by sex.

This paragraph reiterates the main finding that mildly assortative social networks likely have little direct effect on group-level prevalence or population-level epidemic dynamics but may amplify individual-level differences up to the group-level.

This paragraph reviews evidence for individual-level differences in TB infection and transmission by sex and emphasizes the importance of new research looking into the nature of TB infectious period.

This paragraph compares results about epidemic dynamics on assorted networks to previous studies.

* 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.

This paragraph discusses main limitations of this study: rewiring changed some potentially important network structural properties, simplistic TB models, unclear what levels of assortativity are across human populations, model parameterization.

|  |  |
| --- | --- |
| **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. | We conducted sensitivity analyses with the algorithm for Sah et al. (2017), which maintains clustering, degree correlation, and other properties affecting transmission dynamics. |
| 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. | Horton study found sex-assortative patterns in many 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. However, some sub-populations (mining, fishing communities may have higher sex-assortativity) and some 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 | There is so much about TB that we don’t know. For example, just now people are starting to think there may be transmission during latent period. If this is true, is it possible that men are more likely to be infectious during the latent period? Future research needed. Overall, it’s likely that real-world is compound of many differences in epidemic rates. |
| Model parameterization is very arbitrary. Why these transmission rates, recovery parameters, etc. | Math models cannot fully capture the complexities of TB, but our parameter ranges are broad to test generalizability of findings. |

Closing paragraph restates main findings, new questions raised by study, and potential applications of research.

This study tested the potential for social mixing patterns and sex-traits 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.

1. World Health Organization. *Global tuberculosis report*. (2018).

2. Neyrolles, O. & Quintana-Murci, L. Sexual Inequality in Tuberculosis. *PLOS Med* **6,** e1000199 (2009).

3. Guerra-Silveira, F. & Abad-Franch, F. Sex bias in infectious disease epidemiology: patterns and processes. *PLoS ONE* **8,** e62390 (2013).

4. Salim, M., Declercq, E., Van Deun, A. & Saki, K. Gender differences in tuberculosis: a prevalence survey done in Bangladesh. *Int. J. Tuberc. Lung Dis.* **8,** 952–957 (2004).

5. Borgdorff, M. W., Nagelkerke, N. J., Dye, C. & Nunn, P. Gender and tuberculosis: a comparison of prevalence surveys with notification data to explore sex differences in case detection. *Int. J. Tuberc. Lung Dis.* **4,** 123–132 (2000).

6. Clayton, J. A. Studying both sexes: a guiding principle for biomedicine. *FASEB J.* **30,** 519–524 (2016).

7. World Health Organization. Addressing sex and gender in epidemic-prone infectious diseases. (2007).

8. Schurz, H. *et al.* The X chromosome and sex-specific effects in infectious disease susceptibility. *Hum Genomics* **13,** 1–12 (2019).

9. Islami, F., Torre, L. A. & Jemal, A. Global trends of lung cancer mortality and smoking prevalence. *Translational Lung Cancer Research* **4,** 327–338 (2015).

10. Centers for Disease Control and Prevention (US), National Center for Chronic Disease Prevention and Health Promotion (US)Office on Smoking and Health (US). How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General. (2010).

11. Davies, P. D. O. *et al.* Smoking and tuberculosis: the epidemiological association and immunopathogenesis. *Trans. R. Soc. Trop. Med. Hyg.* **100,** 291–298 (2006).

12. Nhamoyebonde, S. & Leslie, A. Biological Differences Between the Sexes and Susceptibility to Tuberculosis. *J. Infect. Dis.* **209,** S100–S106 (2014).

13. Dodd, P. J. *et al.* Age- and Sex-Specific Social Contact Patterns and Incidence of Mycobacterium tuberculosis Infection. *American Journal of Epidemiology* **183,** 156–166 (2016).

14. Systematic Review and Meta-Analysis of Sex Differences in Social Contact Patterns and Implications for Tuberculosis Transmission and Control. *Emerg. Infect. Dis.* **26,** 910–919 (2020).

15. Watkins, R. E. & Plant, A. J. Does smoking explain sex differences in the global tuberculosis epidemic? *Epidemiol. Infect.* **134,** 333–339 (2006).

16. Lindsley, W. G. *et al.* Quantity and Size Distribution of Cough-Generated Aerosol Particles Produced by Influenza Patients During and After Illness. *J Occup Environ Hyg* **9,** 443–449 (2012).