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

**Study narrative**: Across the world, more cases of TB are reported among men than women. Hypotheses for this pattern encompass population- and individual-level differences in the 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 previous explanations for sex-bias have never been systematically assessed alongside each other in a model. Additionally, understanding drivers of male-bias might improve case-finding or other 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: There is a strikingly consistent pattern of male-bias in global TB cases.

Niche: Assortativity and heterogeneity in infection by sex are two mechanisms proposed to drive male-bias

Occupy niche: We developed a model to assess relative importance in driving male-bias of assortativity and heterogeneity in infection by sex.

**Methods:**

1. To simulate synthetic, human, social networks, scale-free graphs with a mean degree of 10 and preferential attachment parameter X were created with the igraph package in R .
2. To generate variation in sex-assortativity of synthetic networks, sex was randomly assigned 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 .
3. 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).
4. 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 .
5. 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 ().
6. 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.
7. 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.

* To understand model output in relationship to real data, global male-bias (called target male-bias throughout results and discussion) and prevalence of latent infection were assessed with information in the 2018 WHO TB Report. Model targets. In 2017, an estimated 5.8 million men and 3.2 million women (M:F ratio 1.8) developed TB disease and 1.7 billion people (23% of the world’s population) were estimated to have latent TB infection.

**Results:**

* Statistics of synthetic networks
  1. 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).
  2. 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)
* Male-bias
  1. 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).
  2. 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.
  3. 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).
  4. 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
  1. 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).
  2. 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.
  3. 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.
  4. At the baseline transmission rates assessed here, assortativity had negligible (or slightly negative) effects on epidemic duration (SIR, SLIR; Fig. 10).
  5. The presence of heterogeneity in infection and transmission at the individual-level had few consequences for equilibrium prevalence in general (Fig. 13).
  6. 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 usually stymied by assorted networks.

Problem items:

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| **Problem** | **Response** |
| TB models are too simplistic, especially the structure of the latent class and lack of age-structure, to accurately make inferences about biological mechanisms | There are multiple ways in which our model could be extended to include more realism in TB life-history. However, our main results (about the relative effects of assortativity and heterogeneity in infection by sex) were not sensitive to model structure or transmission rates suggesting generalizability. |
| Re-wiring algorithm changes some aspects of network structure that may affect disease spread | To inject assortativity into synthetic networks, edge re-wiring was performed. Unfortunately, this algorithm disrupted some network structural statistics and could slightly affect our results about population-level epidemic dynamics, especially for high levels of assortativity. |
| There are few studies that explicitly measure Newman’s assortativity coefficient for preferential mixing by sex across populations making it difficult to know where most populations fall on this range |  |
| There is no evidence that heterogeneities in individual-level infection dynamics exist to the magnitude suggested in this analysis |  |
| None of the parameter combinations lead to high prevalence of latent infection | --- |
| It’s possible that the nature of interaction between men and women are more intimate than within-sex interactions, possibly negating the effect of assortativity. |  |