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

**Story**: 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.

**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 structural modeling assumptions affected results, we performed simulations of pathogen spread on networks with four distinct modeling structures based on a Susceptible-Latent-Infectious-Recovered-Susceptible (SLIRS) and three levels of transmission .
5. To understand the potential effects of assortativity on male-bias relative 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.
8. To understand model output in relationship to WHO estimates, simulated values of male-bias and prevalence of latent infection were plotted against WHO estimates from Uganda.

**Results:**

* The re-wiring algorithm produced networks of desired levels of assortativity with minor changes to clustering, degree assortativity, and path length at lower levels of assortativity. At higher levels of assortativity, assorted networks have slightly higher clustering, degree assortativity, and path length which could alter epidemic dynamics such as …