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The role of sex differences in the prevalence and transmission of tuberculosis

Allison S. Rhines*

Stanford University, Department of Biology, Gilbert Hall, Stanford, CA 94305-5020, United States

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SUMMARY

Tuberculosis (TB) epidemiology is characterized by significant differences in prevalence between men and women worldwide, with cases among men exceeding those found in women by a ratio of 2:1 in some regions. In this paper, we review the literature concerning differences in TB prevalence by sex, as well as arguments that have been offered to explain these differences. We conclude that, while under-reporting and latent variables undoubtedly bias the observed differences in prevalence between males and females to some degree, there is also strong evidence that sex-based differences in TB prevalence represent real epidemiological differences. Such differences have implications for models of TB dynamics in countries with skewed population sex ratios such as China and India, and should be incorporated into models for TB control and forecasting.

With approximately 2 billion latent or active infections,[1] and between one and two million annual deaths worldwide,[2] TB is among today's most serious global health concerns. In the developing world, major global health organizations see TB as a critical public health challenge, and are heavily invested in reducing TB-related mortality and morbidity. There is also growing concern about the spread of drug resistant TB in major developing cities.[3–5] In the developed world, TB has made a recent resurgence among select populations.

1. Human demography and infectious respiratory disease transmission

In a world where population is growing rapidly, intra-and international labor migration rates are increasing, and some nations are struggling to deal with distorted age structures and highly skewed sex ratios, the role of human demography in infectious disease transmission dynamics is an increasingly pressing question. By modeling the effects of age structure on infectious respiratory disease transmission, for example, Chen et al. were able to conclude that certain cities were more vulnerable to infectious respiratory epidemics than others, based on their age structure.[6] Concerning the influence of demographic factors on TB transmission specifically, Brooks-Pollack and colleagues assert that "previous work has focused on the complex natural history of TB…In contrast, there has been little attention and no consensus on the inclusion of demographic patterns that determine age structure."[7] While Brooks-Pollack et al. have constructed a theoretical model for the effects of age structure on TB transmission, research on the effects of other aspects of demography on TB transmission dynamics is still limited.[7]

One aspect of population structure that has not been extensively investigated with regard to TB transmission and generation of secondary cases is population sex ratio. Not only are there interesting and unresolved questions from a theoretical perspective, but many of the countries in which TB is a serious problem have high or rising sex ratios, making them also very important from a global health perspective. India and China, for example, have the largest numbers of TB cases in the world, together accounting for 40% of the world's total notified TB cases.[2] They also have two of the most severe sex ratio imbalances at birth.[8–10] Additionally, both China and India have become centers for TB drug resistance, with large case numbers of both multi-drug resistant TB (MDR-TB) and extensively-drug resistant TB (XDR-TB) in China.[5] The Beijing strain of TB is now globally present.[11–13] Indian scientists recently announced the appearance of totally drug resistant TB in India.[14] Differences in MDR-TB (multi-drug resistant TB) transmission between men and women could seriously complicate the dynamics of these epidemics. If population sex ratio is a factor in TB transmission dynamics, these findings could have implications for TB control strategies in China and India.

2. The role of sex ratio in the TB epidemic

The global TB epidemic is characterized by significant differences in prevalence between men and women. That rates of TB are

* Tel.: +1 650 725 7727.
E-mail address: arhines@stanford.edu.

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much higher among men than women in large areas of the world has been extensively documented.[15] Nevertheless, some scholars believe that these differences are in part, if not wholly, due to the effects of confounding variables such as differential access to care, which would bias case reporting. In this section, we describe the state of the TB epidemic with regard to sex ratio. In the following section, we present arguments from scholars who raise cautions about ascribing importance to the sex ratio in relation to TB.

Borgdorff et al. provide compelling evidence that sex differences in TB prevalence represent real epidemiological differences, and are not merely a product of differences in access to healthcare. Using survey data from 29 studies in 14 countries around the world, Borgdorff et al. found greater numbers of TB cases among men than women in almost all cases. In some world regions, such as Southeast Asia, and the Western Pacific, TB case rates were twice as high in males as in females.[15] While the authors caution that some of the Asian data may have been vulnerable to reporting biases,[15] the trend is still consistent with male to female ratios in other studies that are unlikely to be affected by such biases.[16]

Martinez et al. examined this finding in a study of TB prevalence in San Francisco during the 1990s. While much of the work on sex differences in TB has taken place in areas of the developing world, efficiency of TB diagnosis and reporting are not expected to vary between men and women in San Francisco. In this study, Martinez et al. found a strikingly higher rate of TB among men than women; the ratio of male to female cases was 2·1:1, with differences between men and women particularly large among US-born individuals aged 45–64. This provides especially compelling evidence of an epidemiological difference between men and women, as in this age bracket women are known to have greater healthcare seeking behavior than men.[16,17] Men also had higher rates of TB than women in HIV negative populations. While this study did not explicitly consider homelessness as a possible confounding factor, the findings concerning HIV led Martinez et al. to conclude that these differences in TB rates may be due to "transmission dynamics rather than…reporting bias."[16]

Another study of TB in San Francisco during the 1990s found that being male was associated with clustering in mycobacterial genetic analyses.[18] This result is consistent with the finding of Martinez et al. that the highest male to female case ratios were observed among individuals in clustered isolates, associated with recent transmission, suggesting either that progression from latent to active disease, or propensity to be infected is higher among members of such groups.[16] Causes rooted in transmission dynamics suggest the need for a model that incorporates sex differences in TB transmission.

Maleness or femaleness may be a factor in the development of drug resistance; however, findings are mixed on the subject. While a global prevalence study did not find sex to be a risk factor for MDR-TB,[19] Hudelson has noted differing rates of compliance with treatment for men and women. The WHO-advised therapy program for TB requires direct supervision of patients as they take their medication, through the strategy known as DOTS (Directly Observed Treatment Short course). Traveling to do this often puts a greater burden on women than men; women are frequently juggling children and household chores.[17] This may lead to lower compliance among women, putting them and their contacts at greater risk for drug resistance.[17,20] An interesting new area of study is whether women comply at higher rates if allowed to administer their medication themselves.

While significant sex differences have been documented in rates of TB prevalence,[15] and may exist in rates at which an infected individual spreads TB, a theoretical epidemic model has not yet been constructed that focuses on differences in transmission, secondary case generation, or susceptibility by sex.

3. Critiques of considering of sex ratio in TB prevalence and transmission

In disentangling possible reasons for sex differences in TB rates, we should first ask whether sex differences in TB cases accurately describe the epidemic, or whether they are only an artifact of reporting bias (Martinez et al., 2000). Second, if it can be established that these differences accurately describe existing TB cases, and thus represent real epidemiological differences, it should be investigated whether these differences are biological in nature, or whether they are mediated by cultural, social, economic, gender, or other variables such as differences in rate of progression from latent to active TB. In this section, we describe arguments that have attempted to attribute putative sex differences to other causes.

4. Arguments that observed sex differences represent only reporting bias

Arguments that published sex differences in TB case numbers do not accurately reflect epidemiological trends, but rather represent underreporting, have generally attributed underreporting to two causes: (1) the inability of women in the developing world to access healthcare of the same quality or to the same extent as men, and associated failure to be tested for TB, and (2) failure of existing diagnostics to accurately detect cases among women.[17,20]

The majority of discussion surrounding women and underreporting has focused on the developing world. For example, one study of TB in Vietnam found that female cases were more likely to go undetected.[21] Similar results have been found across East and Southeast Asia. Underreporting in women in developing regions may be due to the inability of women to access healthcare, for a variety of reasons, including competing demands of work in and outside the home, or apprehension around getting tested for fear of social stigma associated with TB, which may be harsher for females than males.[17,20,22] This argument is weakened by data presented in a 2010 study in Vietnam by Hoa et al., which found that even though TB cases in women were significantly more likely to be reported than those in men, the male to female prevalence of TB was 5.1:1.[23]

Some investigation of the differential effectiveness of diagnostics in men and women has been undertaken in the past concerning tuberculin skin test, and more recently, the sputum smear test. One study in Japan in the early 1990s found that the widely used tuberculin skin test was less sensitive in women in this particular population.[24]

More recent work has focused on exploring possible gender biases in effectiveness of the sputum smear test. In a study comparing the accuracy of the sputum smear test among suspected TB carriers in Bangladesh, Khan et al. found that women completed the test incorrectly at much higher rates than men, giving inaccurate samples. When one group of women was given detailed instructions concerning how to properly give a sample, the disparity between men and women was reduced significantly in this population.[25]

The need for access to rapid and accurate diagnostics is pressing. Significant investment in research on more accurate and efficient diagnostics will hopefully clarify the extent to which sex biases in TB are influenced by the power of available diagnostics.

5. Arguments attributing sex differences to confounding with third variables

Confounding factors have been discussed extensively as causes of differences between men and women in TB rates. Two of the most commonly discussed are higher rates of smoking, and of HIV

among men, both of which have been associated with TB. The issue of confounding with HIV is addressed by Martinez et al. in their study of TB in San Francisco. As discussed in the previous section, in San Francisco from 1991 to 1996, TB rates were higher among men than women, even in HIV-negative populations.[16]

Hudelson suggests that sex differences may exist in risk of infection, citing the fact that in many societies, men have more social contacts due to work outside the home. He concludes however, that while TB prevalence is consistently weighted toward males across the world, social contacts very significantly between cultures, suggesting that underlying biological factors are likely to be at work.[17]

While such confounding factors may be important in the wider fight to eradicate TB, they are not of critical relevance to theoretical models of sex differences in TB transmission. Such models should consider the real epidemiological differences in TB rates between men and women, rather than the sources of those differences, whether biological, cultural, social, or economic.

HIV-modulated TB dynamics are particularly interesting for the purpose of studying TB and sex ratio, as such interactions will undoubtedly be further complicated by sex differences in HIV/AIDS prevalence and transmission. Comparisons of HIV/AIDS caseloads between men and women vary by region of the world.[26] Models for the interaction between population sex ratio and HIV/AIDS prevalence predict that male-biased sex ratios will be associated with increased rates of HIV in such populations.[27] Masculinized sex ratios, then, in addition to directly affecting TB transmission, might further complicate disease dynamics indirectly via gender differences in HIV/AIDS prevalence.

6. Arguments that sex differences only represent differences in disease progression

Related to the argument that TB transmission is modulated by third variables is the idea that such variables modulate not just transmission of TB, but progression from latent to active TB.[17] Several studies have suggested that significant sex differences exist in progression from latent TB to active disease. A number of studies in different populations have found that women have higher rates of progression to disease during reproductive years, while men have higher rates of progression to disease during later years in life.[17,20] One study, however, found that among European Americans, males had higher rates of disease progression than females at all ages.[20] On the whole, studies concerning disease progression have conflicting results; this area requires further research.

7. Conclusions and implications

Based on the evidence presented, we believe that an epidemiological sex bias in TB is a distinct possibility. Whether such a sex bias might be due to biological or cultural factors or both, it would have serious implications in a modern demographic context. While research suggests that a large number of undetected cases of TB among women in the developing world probably exist, the presence of undetected TB among women, is not in itself strong evidence that men and women are equally susceptible to TB. Although the difference in HIV prevalence is frequently cited as a modulator of the effects of sex on TB susceptibility, the fact that TB was shown to be more prevalent in men than women among HIV negative individuals,[16] suggests that TB is certainly a gender-biased, and probably a sex-biased infection and that there is a need for epidemiological models incorporating sex-based difference in TB prevalence and transmission.

The importance of taking sex-based differences into account would be particularly acute in areas with skewed population sex ratios, such as China and India. China in particular, is experiencing not only heavily skewed sex ratios at birth, but distorted age structure and massive rural-to-urban migration. India and China have the two largest numbers of TB cases in the world; effects of skewed population sex ratio could have implications for TB epidemic forecasting and control strategies in countries where TB cases are most numerous. Moving forward, epidemic forecasts in countries occupying a critical place in the global TB fight against TB such as India and China should take account of the potential effects of skewed population sex ratios in these countries.

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