Sex Bias in Tuberculosis in the Developing World

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ABSTRACT
Tuberculosis (TB), the most deadly global single organism infectious disease, kills nearly twice as many men as women. Understanding the factors that drive this bias in TB mortality is an important aspect of the global effort to reduce the enormous burden of this disease in the developing world. One third of the world's population is estimated to be infected TB, with Low and Middle Income Countries (LMIC) bearing the greatest disease burden. In LMIC sex bias in TB is influenced by sociocultural, behavioural as well as biological factors, with dynamic interactions between reporting variables, other confounding variables and physiological mechanisms, which each influence one another to produce the male-biased sex ratio observed in TB transmission, prevalence and mortality. While confounding factors are addressed in the existing global drive to tackle TB it is the biological aspects of sex bias in TB that present specific challenges for diagnosis and treatment in men and women as they potentially influence future immunological-based interventions to treat TB.

INTRODUCTION
Global prevalence of tuberculosis
One third of the world's population is estimated to be infected with latent tuberculosis (TB), with 10% progressing to active infection over their lifetime. In 2017, 10 million people fell ill with TB, with 1.3 million deaths.[1] Globally, TB is one of the top 10 causes of death and the leading cause of death from a single infectious agent (above HIV/AIDS). While Africa has the highest incidence rate of TB (236 cases per 100,000 people in 2017) the majority of patients with TB live in the most populous countries of Asia (52%).

TB incidence is correlated with a weak immune system, as this increases the chance of active infection.[2] Factors which increase the chance of active infection are: HIV, malnutrition, smoking and alcohol abuse, and are all associated with living in a LMIC. The common pattern of migration seen in LMIC from rural to highdensity areas, increases transmission rates.[3] Even though a re-emergence of TB in LMIC is related to migration of young adults, the age class with the highest TB rates are adults over 45 years old due, in part, to birth rate decreases as longevity and education improve in LMIC.[4] There has been a resurgence of TB in Eastern Europe since the 1990s with the fall of the Soviet Union and subsequent economic decline and political instability that resulted in an inadequate public health approach to TB control. Limited and substandard quality first and second-line drugs contributed to the increase of multi- and extensively-drug resistant TB (MDR- and XDR-TB) in Eastern Europe. MDR-TB are strains of TB which are resistant to at least two front-line drugs: isoniazid and rifampicin, while XDR-TB is additionally resistant to any fluoroquinolone and at least one injectable second-line drug (i.e. amikacin). Currently, only 3% of the global burden of TB but 20% of the MDR-TB is found in the European region, primarily Eastern Europe.[1]

In Africa, the rapid rise in HIV infection rates in the 1980s contributed to the resurgence of TB on the continent.[5] Normally only 5-10% of infected individuals develop TB in their lifetime, however when co-infected with HIV the risk of reactivating a latent TB infection increases to 5-15% annually.[6] In 2017, 1 in 3 HIV deaths were due to TB and globally 9% of TB cases were co-infected with HIV.[1] The main factor associated with TB recurrence in people living with HIV in Africa was baseline CD4 count.[7] There is significantly lower HIV-specific T-cell function in co-infected individuals compared with HIV mono-infected individuals, which means that the TB bacilli are not restricted to a few infected macrophages. This results in an increased HIV disease progression in TB/HIV co-infected individuals and reactivation of latent TB.

Sex bias in TB epidemiology has been shown to be influenced by many variables including HIV disease progression, as HIV disproportionately impacts young women aged 15-24 years.[8] Social sexual inequality can also influences rates of MDR-TB, as shown in China where its severe sex ratio imbalances at birth[9] have almost certainly influenced its development as a centre for MDR-TB and XDR-TB.[10] Also differences in MDR-TB transmission between the sexes could have an additional impact on these dynamics.

What role does sex bias have on the global tuberculosis epidemic?

Tuberculosis is about twice as prevalent in men as in women (**Figure 1**), with a global male:female sex ratio for TB of 1.7:1 in 2017. Countries with the highest ratios are globally spread, from El Salvador (3.2:1), The Gambia (2.6:1), Moldova (2.5:1) and the Philippines (2.4:1).[1] Sex bias is historically attributed to epidemiological factors, such as cultural and socioeconomic impacts leading to barriers in accessing healthcare.[11] However, the definitive cause of this bias is unknown but biological differences between the sexes are shown to affect susceptibility to mycobacterial infection.[12]
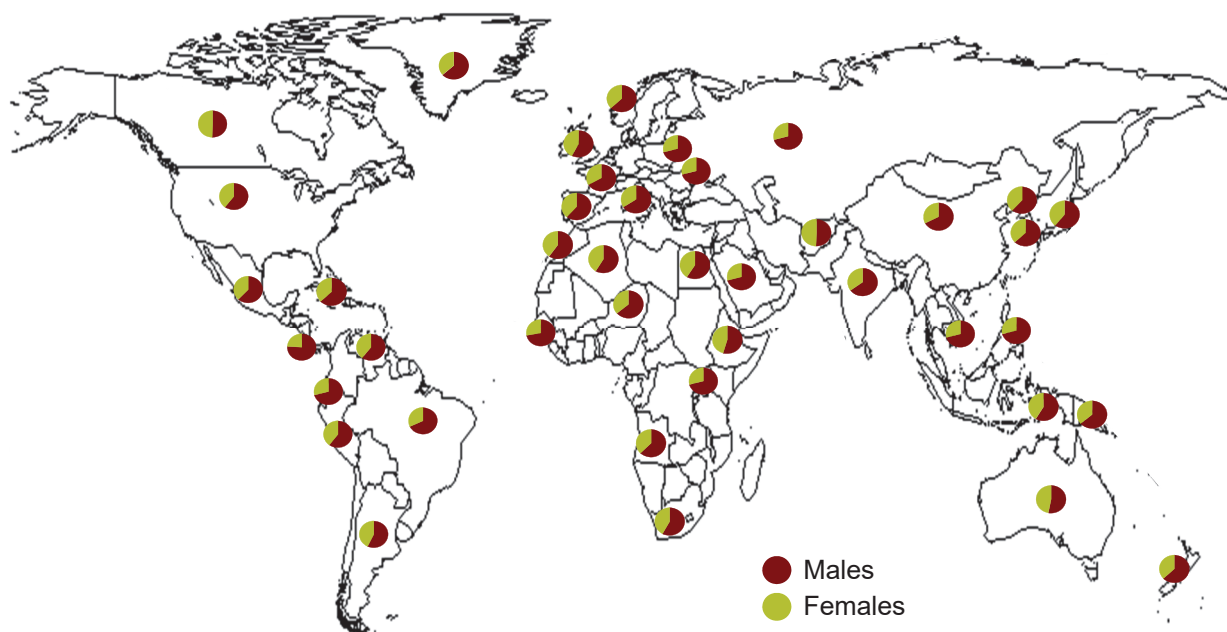
Figure 1. Global sex distribution for new cases of TB in 2017.[1] Males (in dark red) have a greater incidence of TB compared to females (in green) in all regions. El Salvador, The Gambia, Vietnam and some Eastern European countries had some of the highest proportions of TB in males (70-76%).

In an analysis of 29 studies in 14 countries, there were more TB cases in men than women in almost all cases[13] which, as studies of sex bias in TB are predominantly undertaken in LMIC, suggest there is an impact of cultural and social factors. It has been reported that Directly Observed Treatment Short Course (DOTS) for TB, which requires direct supervision of patients taking medication, can result in a greater risk of drug resistance and transmission to contacts among women as some are unable to travel as often as needed to the DOTS clinic.[14] However, a recent global study concluded that sex was not a risk factor for MDR-TB.[15] Given that confounding variables like access to clinics have been shown to affect the viability of treatment[16], the incorporation of progressive treatment of TB into practice, such as working towards women patients administering their own medication, is important.

Studies in High Income Countries (HIC) like the USA can controlled for reporting bias and so enabled trends due to biological differences between the sexes to be examined. One such study by Martinez et al.[17] still showed a higher incidence of TB in men than women (2.1:1) even in HIV-negative populations, with the highest sex ratio in 45-64 year old adults. This is an age group when women are more likely than men to access healthcare[14] so more likely to be identified as TB-positive, hence this study shows real epidemiological differences between the sexes. In addition, Martinez et al.[17] found that the highest sex biases seen were in clusters of patients, meaning that within these clusters there is a higher chance of infection and higher rates of progression from latent to active infection. This conclusion was supported by Cattamanchi et al.[18] who showed that being male was linked with clustering in mycobacterial genetic analyses. These studies conclusively state that differences they detected in TB rates were due to the dynamics of TB transmission and not reporting bias.

Is there evidence that reporting bias affects the sex ratio in tuberculosis?

Healthcare in LMIC is often less accessible to women, due to factors such as childcare and inability to travel alone to appointments[19] leading to the suggestion that, in some cases, the epidemiological differences seen between the sexes could be due to reporting bias rather than biology. There is evidence that existing methods of TB detection have higher failure rates in women.[16] Specifically, the most widely used detection method, the tuberculin skin test, is less sensitive at detecting TB in women than in men[12] and in a randomised trial of TB detection by the sputum smear test found that women completed the test incorrectly significantly more often than men.[20] However, when the instructions for the sputum smear test were clearer, the gap in TB notification rates between the sexes was reduced. In addition, men with a cough were significantly more likely to receive a sputum smear examination than women.[21] Studies in Vietnam have found that female cases were significantly more likely to go undetected, with women being diagnosed on average two weeks later than men due to delays from healthcare providers.[22] These results highlight how, on average, TB notification rates are lower for women than for men even when in contact with healthcare providers.

Conversely, in studies where reporting bias is either eliminated or less likely, there are still clear epidemiological differences between the sexes in prevalence of TB. A study carried out in South India using a report from a rural DOTS programme, found that even though men had higher rates of TB, women were significantly more likely to access healthcare services, be notified under DOTS and comply with full treatment.[23] A national survey in Vietnam found that even though TB cases in women were more likely to be reported than male TB cases, the male to female ratio was still 5.1:1.[24] In these particular studies women had higher access to healthcare, but men still had higher rates of TB cases. In these populations the disparity of prevalence of TB between the sexes must be mostly biological, so is there clear evidence to support a physiological difference between men and women in the prevalence and progression of TB?

Do sex differences only affect disease progression of TB?

Sex bias seen in TB cases may be partly due to differences in disease progression from latent to active TB infection rather than initial transmission of TB. It has been reported that women have higher rates of progression to active infection during their reproductive years, while in men higher rates of progression to active TB occur in their later years of life.[14,25] There are many possible reasons for higher rate of disease progression among young women in their reproductive years. Stresses of pregnancy as well as the natural depression of immune function in order to protect the foetus can contribute to disease progression. However, studies, including case controlled studies, have failed to show a link between pregnancy and TB.[26-28] Newly infected people have a greater chance of progression to active infection than those with an older infection.[29] Higher rates of progression to active TB in reproductive-age women could be linked to the lower rates of TB cases in adolescent women compared to adolescent men. Therefore, women are more likely than men to be newly infected during their reproductive years and so more likely to progress to an active infection. In addition, higher rates of progression to active TB infection among older men could be due to sex specific variables, such as smoking or heavy alcohol consumption, which are more common in men and can lead to reduced immune function and increased disease progression of TB.[30] Thus, evidence shows that women in their reproductive years have higher disease progression than men, so the lower notification rates seen for women appear not to be due to a lower disease progression to active TB.[13]

Can the sex ratio be attributed to confounding variables?

Confounding variables could be the basis of sex bias leading to differential TB rates between men and women. Behaviour has been proven to affect exposure to TB, with men more likely to have a greater number of social contacts and, in LMIC, have professions with higher risks of infection, such as mining, compared to women.[31] Household contact with infected individuals is a strong risk factor for TB[32] but even though women typically spend more time at home in LMIC, men still remain at a higher risk of acquiring TB from a household contact.[33]

The prevalence of HIV/AIDS varies by region and between men and women (UNAIDS, 2014). HIV has been discussed as a variable which impacts differential TB incidence between the sexes in a study carried out in San Francisco. As discussed above, TB rates were higher among men than women even in HIV-negative populations in a study that eliminated reporting bias.[17] HIV/TB co-incidence dynamics can give an insight into sex bias, and can also be influenced by the sex differences seen in HIV/AIDS prevalence. A review on TB sex bias and transmission of HIV in Shanghai found that TB infections of men are linked to higher rates of HIV in the population.[34] From this it is clear that there is a viable case for sex differences potentially affecting TB transmission and the interaction between TB and HIV/AIDS. Fifteen percent of women living with HIV are 15-24 year olds and 80% live in Sub-Saharan Africa. As HIV disproportionately affects young women in Africa, it is critical to investigate whether this variable influences TB disease dynamics in reproductive women. A study in Tanzania found that HIV infection among smear-positive TB cases was higher in women than men in the 15-34 years age range.[35] In Zambia it was found that 74% of women aged 14-24 years were HIV-positive compared to 48% of men of the same age. After 24 years of age, there was a higher number of male TB cases, but the prevalence of HIV was similar in all people with TB.[36] These results show the sex

bias seen in TB in the presence of HIV, and demonstrates that even in cases where HIV is more prevalent in women, TB cases are still higher in men.

Confounding variables, like behaviour, HIV and pregnancy can affect TB disease dynamics. These variables can lead to an increased rate of transmission, as well as increased TB disease progression. The co-related disease dynamics. The implementation of TB testing in HIV clinics could result in increased numbers of successful TB treatments. As much is still unknown regarding the disease dynamics of TB and HIV, and their interactions, diagnostics in low resource clinical settings need to improve rapidly.

Physiological mechanisms of sex bias

While analysis of behaviour offers some explanation for the sex differences seen in TB transmission and prevalence, analysis of physiology provides stark evidence for how biological differences between the sexes result in men being more susceptible than women to TB infection, as well as an explanation for increased disease progression seen in men.

Sex-specific gene architecture

Sex-specific gene architecture has been demonstrated to have a major effect on susceptibility to TB infection and disease progression in humans[37], while the use of rodent models has enabled investigation of specific genes known to respond to mycobacterial infection.[38] Genome-wide linkage analyses have identified dominant loci on chromosome 8 and the X-chromosome that appear to confer a predisposition to TB in adults.[39,40] Polymorphisms of the transport protein NRAMP1 were linked to reduced TB susceptibility in young adult women[41] and that the risk of developing TB was linked to polymorphisms in specific toll-like receptors (TLR), which are responsible for cellular recognition of microbial structures and so influence immune response to infection.[42] X chromosome-linked TLR8 gene polymorphisms have been linked to susceptibility to TB infection especially in male children[43] and 2 other X-chromosome linked genes, *IKBKB* and *CYBB,* are part of a group of 9 genes known to be associated with susceptibility to mycobacterial disease.[44] Gene-dosing effects in women have been proven to be beneficial in terms of reduced TB susceptibility as about 15% of X-linked genes can escape silencing. This can lead to the increased expression of these genes in women[45], including immunomodulatory micro-RNAs (miRNAs), which are far more numerous on the X chromosome compared to the Y chromosome.[46] It is clear that investigation of expression of X-linked genes and miRNAs could lead to a better understanding of sex-specific susceptibility to TB infection.

The role of Sex steroids and nutrition in differential TB susceptibility.

In many infectious diseases females exert a greater immune response to foreign antigens than males[44], with sex steroid hormones playing a role in this differential immune responses (**Figure 2**[11,47]). Therefore, sex hormones could be a significant factor for sex bias in TB. Testosterone impairs pro-inflammatory cytokine production[48], whereas oestrogens are a pro-inflammatory inducer.[49] In TB-infected mouse models, non-castrated males had higher mortality, higher bacilli burdens, less inflammation in lung compartments and lower cytokine production compared to female and castrated male mice.[50]

Activated macrophages are thought to have an important role in the immune response to TB infection through the destruction of *M. tuberculosis* (Mtb) bacilli.[51] While the oestrogen sex steroid estradiol enhances macrophage activation[52], testosterone reduces macrophage activation through down-regulation of TLR4 expression.[44] Apoptotic cell death of Mtb-infected macrophages is vital for Mtb control and decreases bacterial growth, whereas necrotic cell death promotes bacterial growth. Apoptotic and necrotic cell death is balanced through the regulation of prostaglandin (PGE2; pro-apoptotic) and lipoxin A4 (LXA4; pro-necrotic) activity.[53] The sex hormone progesterone can increase PGE2 production by monocytes, while testosterone inhibits PGE2 production[54] suggesting sex differences in macrophage regulation and a basis for sex differences in TB infection and progression.

While macrophages appear to have a central role in TB immune response, neutrophils are thought to be the dominant infected cell type in the upper respiratory tract during active TB.[56] Lyadova[57] suggested that TB disease dramatically alters neutrophil population, leading to the accumulation of heterogeneous subsets of immature and activated dysfunctional cells and a decline in true neutrophils. Interferon (IFN) secretion is shown to be driven by neutrophils in active TB infection.[58] Mice lacking IFNγ or the IFNγ receptor showed increased susceptibility to Mtb infection through increased recruitment of Mtb-infected neutrophils into the lungs,[59] highlighting the importance of IFNγ in TB. Neutrophil recruitment can be modulated by miRNA, particularly the X-chromosome linked miRNA-223 which downregulates CXCL2 and CCL3 in neutrophils, and so reduces their recruitment into lungs. Deletion of miRNA-223 results in increased susceptibility to Mtb infection due to pathogenic neutrophil recruitment in the lungs, leading to tissue damage.[60] Incomplete gene silencing in females often leads to higher expression levels of miRNA-223 and so lower pathogenic recruitment of neutrophils compared to males. Progesterone and oestrogen decrease spontaneous neutrophil apoptosis in females,[61] whereas testosterone increases neutrophil activation in males.[62] Sex steroids have also been linked to structural and histological differences of the upper airway and respiratory tract between the sexes.[63,64] Therefore, understanding the influence of sex steroids on immune responses and physiology are critical to determining the biological basis of sex bias in TB.
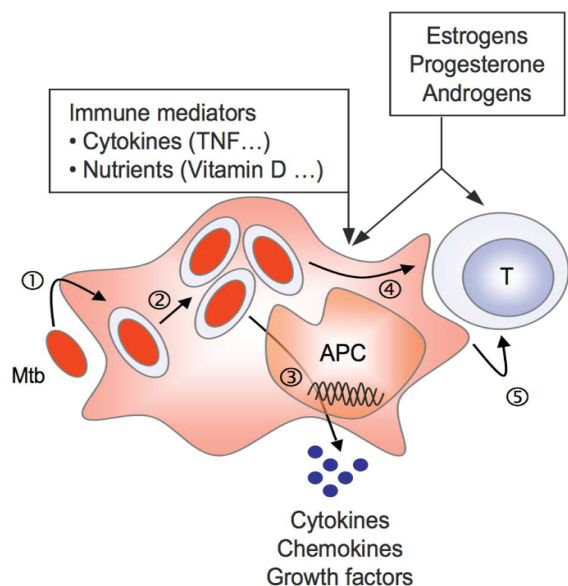
Figure 2. How sex steroids influence mycobacterial immunity. Immune cells and T-cells express receptors for steroid hormones on their cell surface.55 Sex steroids can influence *M. tuberculosis* (Mtb) entry (1) and intracellular trafficking (2) in host phagocytes and antigen-presenting cells. Sex steroids can modulate the secretion of cytokine and growth factors by Mtb infected cells (3), can result in antigen presentation (4) and T-cell development (5). Figure taken from Neyrolles & Quintana-Murci (2009).[11]

Nutrition and metabolism could impact the susceptibility to Mtb infection, as sex differences in nutrition can be linked to immune function.[65,66] In the developing world malnutrition is a major concern, for example, iron deficiency in women is an important issue in LMIC.[67] Studies have shown that iron overload increases susceptibility to Mtb infection, both *in vivo*[68] and *in vitro*.[69] Iron is a critical component of microbial enzymes and redox systems[70] and has been linked to immune system mechanisms to control pathogens, such as mycobacteria.[71] Vitamin D has been reported to mediate an antimycobacterial response through the triggering of TLRs[72] and oestrogen has been linked to vitamin D-mediated resistance.[73] A case-control study among Gujarati Asians living in west London, UK, found that vitamin D deficiency and receptor polymorphisms had a major influence on susceptibility to TB.[74]

Sex differences in treatment
As physiological differences between the sexes can result in differential susceptibility to Mtb infection and progression to active infection, it is possible that treatment would have different outcomes between the sexes due to sex-specific mechanisms as well. For example, a Ugandan study investigating sex differences in the presentation and outcomes of HIV-infected adults with TB, found that there were differences of TB incidence rates between the sexes at presentation. However, 1 year after the start of TB treatment outcomes were similar, suggesting there were no differential treatment effects between men and women.[75] In contrast, a study in West Bengal, India, found there was a statistically significant difference between treatment outcomes in men and women, with more women successfully treated compared to men.[76] In both of these studies, confounding factors were eliminated indicating it is still unclear whether sex-bias influences success rates in TB treatment.

Social factors can also influence treatment outcome, as completion of TB treatment has been reported to be affected by various factors including sex and impact of HIV/AIDS[77], although these data are somewhat contradictory. Hudelson[14] reported lower treatment compliance of women compared to men as women were impacted more severely by the stigma associated with TB. In contrast, a four-country (Bangladesh, India, Malawi and Colombia) WHO study found that there were higher dropout rates in men than women due to distress caused by fear of stigma and rejection.[78] Financial impact, hospitalization due to the disease and difficulties in attending clinics during opening times are suspected to be major causes for failure in TB treatment completion in men[23] and higher dropout rates among males than females were also reported in a more recent study in Taiwan.[79]

A systemic review of qualitative research highlighted major social and cultural factors which influence TB treatment outcome, including poverty, gender discrimination and health service factors.[77] This review found a correlation between the patients' understanding of the treatment and a positive treatment outcome. In this review women were more motivated to adhere to treatment, which aligns with reports from other studies on health-seeking behaviour. Failure to complete first-line treatment is linked to the development of drug resistant Mtb strains. Previous treatment with a second-line injectable drug is the strongest risk factor for XDR-TB[80], however various studies have linked being female as another major risk factor for MDR and XDR-TB.[81,82]

Treatment needs to be offered in ways that maximises patient adherence to improve positive TB treatment outcome rates. Social factors due to work schedules of men and fear of stigma for women need to be considered and addressed, in order to provide appropriate interventions for both sexes and reduce treatment dropout rates. Physiological mechanisms of sex bias need to be better understood so that healthcare providers can offer optimal treatment for each sex to improve cure rates.

CONCLUSION

Despite recent efforts TB is still a leading cause of death worldwide, killing more than a million individuals each year. Though seemingly dormant in developed countries since the introduction of the BCG vaccine in the 1950s, TB re-emerged in parts of Europe and the developing world due to various confounding variables. The rise of HIV in Africa in the 1980s led to a rapid rise in TB rates, while socio-economic decline from the fall of the Soviet Union in the 1990s resulted in poor living conditions and healthcare provision, leading to MDR/XDR-TB. With increasing global migration and mobility between regions a rise in TB notification rates in the developed world is likely to occur in the future.

The 2018 WHO Global TB report, documented a staggering 54 million lives saved between 2000 and 2017 due to effective diagnosis and treatment, alongside a 42% drop in mortality due to TB.[1] The evidence discussed here points to an epidemiological sex bias in the transmission and prevalence of tuberculosis. A complex mixture of biological and cultural factors underlie a stark differential susceptibility to TB infection and progression to disease between males and females. Reporting bias due to cultural factors can contribute to lower notification rates of TB infection in women[19], however reporting bias is not strong enough to explain the differences in male and female susceptible to TB. HIV is known to modulate TB susceptibility[5], so high rates of HIV in regions such as Sub-Saharan Africa[83] are likely to influence TB rates in these populations. However, higher TB rates in men than women in HIV-negative populations[17] show that sex bias is important in TB epidemiology.

Much work needs to be done to understand the relationship between sex and TB, as the physiological mechanisms behind immune responses and immunity to TB in men and women are unclear. It is highly likely that there is an interplay between physiological mechanisms influenced by sex-specific gene architecture, differential immune responses, and nutrition alongside confounding variables influenced by cultural factors, HIV prevalence, and MDR/XDR-TB prevalence, which are responsible for the male-biased sex ratio reported globally in TB. Improved knowledge of the role of sex steroid hormones in immunity will greatly improve understanding of how sex influences resistance to TB.

The WHO End TB Strategy plans to end the global TB epidemic, with targets to reduce TB deaths by 95% and to cut new cases by 90% by 2035.[1,84] Reaching these targets could be assisted by immunological and epidemiological research of sex bias. These future developments could impact the intervention of vaccines and other immunological approaches to improve TB cure rates, and ultimately lead to better education and knowledge of TB transmission and disease progression between the sexes, resulting in improved TB notification rates in men and women and a more effective strategy to tackle TB globally.

ACKNOWLEDGEMENTS

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PRESS SUMMARY
One third of the world's population is estimated to be infected with tuberculosis (TB), a disease that affects twice as many men than women. We consider the different sociocultural, behavioural and biological factors that may produce this bias and consider how this might affect TB Transmission and progression and the possibility of exploiting these sex differences to better target TB treatments.