

## **A Bayesian approach to understanding gender differences in tuberculosis disease burden**

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## ABSTRACT

Globally, men have a higher epidemiological burden of tuberculosis (incidence, prevalence, mortality) than women, possibly due to differences in disease incidence, treatment initiation, self-cure and/or untreated-tuberculosis mortality rates. Using a simple, gender-stratified compartmental model, we employed a Bayesian approach to explore which factors most likely explain men's higher burden. We applied the model to smear-positive pulmonary tuberculosis in Viet Nam in 2006-07 and Malawi in 2013-14. Posterior estimates were consistent with gender-specific prevalence and notification data in both countries. Results supported higher incidence in men and showed that both genders faced longer durations of untreated disease than estimated by self-reports. Prior untreated disease durations were revised upwards 8- to 24-fold, to 2.2 (95% credible interval: 1.7, 2.9) and 2.8 (1.8, 4.1) years for men in Viet Nam and Malawi, respectively, approximately a year longer than for women in each country. Results imply that substantial gender differences in tuberculosis burden are almost solely attributable to men's disadvantages in disease incidence and untreated disease duration. The latter, for which self-reports provide a poor proxy, implies inadequate coverage of case finding strategies. These results highlight an urgent need for better understanding of gender-specific barriers faced by men and support the systematic targeting of men for screening.

Keywords: access to health care, Bayes theorem, gender, incidence, mathematical model, sex, time to treatment, tuberculosis

Abbreviations: CI, confidence interval; CrI, credible interval; IHME, Institute for Health Metrics and Evaluation; WHO, World Health Organization

Substantial gender disparity exists in the burden of tuberculosis, as indicated by incidence, prevalence and mortality estimates. Each year, more tuberculosis cases are reported among men than women globally and in most countries (1). Prevalence surveys, which provide the most reliable source of data on tuberculosis burden (2), show even greater gender disparity, with a two-fold higher underlying burden of undiagnosed disease among men than among women in low- and middle-income countries (3). Comparisons of these two measures using prevalence-to-notification ratios (4) imply that gaps in the detection and reporting of new cases are greater for men than for women (3, 5). Yet discussions of gender and tuberculosis tend to focus on and prioritize the needs of women (6-9), often highlighting women as a key population with need for improved access to tuberculosis services (6-8).

Gender disparities in the epidemiological burden of tuberculosis could be explained by gender differences in four factors: disease incidence, treatment initiation, self-cure and/or untreated-tuberculosis mortality rates. Individuals are added to the pool of prevalent cases upon development of incident disease, and disease incidence rates could differ between men and women due to gender differences in exposure to infection and/or susceptibility to disease. Diseased individuals are then removed from the prevalent pool by successfully initiating treatment, naturally clearing themselves of disease (“self-cure”) or dying (10), rates of which may differ by gender due to biological and/or socio-behavioral factors. Existing evidence suggests that there may be gender differences in disease incidence and treatment initiation rates, while there is no evidence to support differences in self-cure or untreated-tuberculosis mortality rates (11).

Using a simple compartmental model (12) of tuberculosis incidence, prevalence and case notification rates, we employed a Bayesian approach to explore which factors most likely explain

the higher epidemiological burden of disease in men. A better understanding of gender differences in the burden of tuberculosis is imperative for the formulation of evidence-based gender-sensitive policies and programs. Implementing such programs at both the global and national level will improve gender equity in access to diagnosis and treatment, as prioritized in the End Tuberculosis Strategy (13) and Sustainable Development Goals (14). Although little attention is placed on men's burden of disease in current gender policies and programs (6-9), addressing gender imbalances in tuberculosis will ultimately benefit men, women and children.

## METHODS

### Data

We conducted analyses for smear-positive pulmonary tuberculosis in two settings: Viet Nam, where the male-to-female ratio in smear-positive tuberculosis prevalence is one of the highest in the world at 5.1:1 (15), and Malawi, where the corresponding gender disparity is less extreme, with a male-to-female prevalence ratio of 2.0:1 (16).

Gender-specific tuberculosis incidence rates were based on 2015 World Health Organization (WHO) estimates of incident cases (age  $\geq 15$  years) (17) and population estimates from the United Nations Department of Economic and Social Affairs (18, 19). Treatment initiation rates for men and women were calculated as the inverse of untreated disease duration based on self-reported time from disease onset to treatment initiation (20, 21), as extracted from literature reviews (Web Appendix 1). Self-cure and untreated-tuberculosis-specific mortality rates were gathered from sources used in previous modelling studies (22-24). Untreated-tuberculosis-specific mortality and background mortality (25) rates were combined to give an overall untreated-tuberculosis mortality rate. Log-normal distributions, which provided the best fit to the

data, were used to describe disease incidence, treatment initiation, self-cure and untreated-tuberculosis mortality rates. Informative priors were chosen so that the middle 95% of expected values fell within the 95% confidence interval or the middle 50% of expected values fell within the interquartile range, as appropriate to available data. Distributions were fitted using Parameter Solver, version 3.0, a software application that solves for the distribution parameters of a random variable given user-defined quantiles (26).

Gender-specific smear-positive tuberculosis prevalence data were collated from national prevalence surveys conducted in Viet Nam in 2006-07 (15) and in Malawi in 2013-14 (16). Case notification rates for smear-positive tuberculosis in men and women were calculated using case notification numbers reported to WHO (1) and population estimates from the United Nations Department of Economic and Social Affairs (18, 19). Confidence intervals for prevalence and case notification rates were based on the normal approximation to the binomial distribution.

Full details of prior specification and data are provided in the Web Appendices 1 and 2, and data on prevalence and case notification rates are shown in Figure 1.

## Model

We developed a simple gender-stratified (male and female) model of disease incidence, prevalence and case notification rates for adult (age  $\geq 15$  years) smear-positive tuberculosis, as shown in Figure 2. (Direct acyclic graphs are provided in Web Figures 1 and 2.) Transition rates for disease incidence, treatment initiation, self-cure and untreated-tuberculosis mortality were used to calculate expected prevalence and case notification rates. Gendered risk factors for infection with *Mycobacterium tuberculosis*, progression to tuberculosis disease and death following infection, notably tobacco smoking in Viet Nam and HIV in Malawi, were not

explicitly modelled, instead being captured as part of overall gender differences in disease incidence and untreated-tuberculosis mortality rates.

The expected prevalence of smear-positive tuberculosis in gender  $g$ ,  $prev_g$ , was calculated as  $prev_g = inc_g / (ti_g + sc + mu)$  where  $inc_g$  is the disease incidence rate in gender  $g$ ,  $ti_g$  is the treatment initiation rate in gender  $g$ ,  $sc$  is the self-cure rate, and  $mu$  is the untreated-tuberculosis mortality rate. The expected case notification rate for smear-positive tuberculosis in gender  $g$ ,  $not_g$ , was calculated as  $not_g = prev_g \times ti_g$ . Male-to-female ratios in expected prevalence-to-notification ratios were calculated.

### Statistical analysis

The evidence described above was used to specify model priors for disease incidence, treatment initiation, self-cure and untreated-tuberculosis mortality for each gender in each country (Table 1 and Table 2 “Model priors”). The model was then confronted with gender-specific data on prevalence and case notification rates (Table 1 and Table 2 “Empirical data”) in a Bayesian framework (27). Posterior model estimates (Table 1 and Table 2 “Model posteriors”) show how prior beliefs about disease incidence, treatment initiation, self-cure and untreated-tuberculosis mortality should be modified in light of the empirical prevalence and notification data. Posterior estimates were examined for consistency with empirical data on gender-specific prevalence and case notification rate, as well as male-to-female ratios in prevalence-to-notification ratios. The model was considered consistent with empirical data if empirical point estimates were within the 95% credible intervals of posterior model estimates.

Posterior model estimates were calculated using Markov chain Monte Carlo algorithm in WinBUGS (28) via R (29) according to code included in Web Appendix 4. Results were based

on three Markov chains of 21,000 iterations; the first 1,000 samples of each chain were discarded as burn-in. Convergence was assessed visually and using potential scale reduction factors (30).

### Sensitivity analyses

We conducted extensive sensitivity analyses, which are described in detail in Web Appendices 5, 6, and 7. We explored our choice of model structure by examining all combinations of fixing individual parameters by gender and allowing individual parameters to differ by gender. We also explored our choice of incidence rate priors using incidence rate priors based on estimates from the Institute for Health Metrics and Evaluation (IHME) (31). Finally, we explored the implications of assuming self-reports of symptom duration prior to treatment accurately describe untreated disease duration.

## RESULTS

Prior model estimates accurately represented evidence on disease incidence, treatment initiation, self-cure rate and untreated-tuberculosis mortality rates (Web Tables 4 and 5).

Posterior model estimates were consistent with empirical data on gender-specific prevalence and case notification rates, as well as male-to-female ratios in prevalence-to-notification ratios, in both countries (Table 1 and Table 2).

In both countries, posterior incidence rate estimates were consistent with empirical data. In Viet Nam, incidence was estimated as (posterior median) 258 (95% credible interval, CrI: 216, 314) per 100,000 men and 67 (95% CrI: 56, 83) per 100,000 women. In Malawi, incidence was estimated as (posterior median) 295 (95% CrI: 218, 410) per 100,000 men and 161 (95% CrI: 118, 235) per 100,000 women.

Posterior estimates for treatment initiation rate showed that both men and women faced much longer time between onset of disease and initiation of treatment than estimated from self-reports of symptom duration prior to treatment (Figure 3). Prior untreated disease durations were revised upwards 8- to 24-fold, to posterior median estimates of 2.2 (95% CrI: 1.7, 2.9) and 2.8 (95% CrI: 1.8, 4.1) years for men in Viet Nam and Malawi, respectively, and 1.0 (95% CrI: 0.6, 1.6) and 1.9 (95% CrI: 1.2, 2.9) years for women, respectively.

In both countries, sensitivity analyses around model structure supported our decision to allow only disease incidence and treatment initiation rates to differ by gender. In these analyses, all scenarios that allowed rates of disease incidence and treatment initiation to differ by gender (regardless of restrictions on self-cure and untreated-tuberculosis mortality rates) were consistent with empirical data (Web Tables 18, 19, 22). When self-cure and/or untreated-tuberculosis mortality rates, in addition to disease incidence and treatment initiation rates, were allowed to differ by gender, posterior estimates were not substantially different from the main analysis (Web Tables 18, 19, 22). In Malawi, posterior estimates from two additional scenarios were also consistent with empirical data (Web Tables 16 and 21). However posterior estimates for untreated-tuberculosis mortality rates among women in these scenarios were over twice those estimated among men, which evidence suggests is unlikely (11). No other scenarios produced posterior estimates consistent with empirical data.

Sensitivity analyses were also conducted using incidence estimates from IHME rather than WHO. Posterior estimates for Viet Nam were not consistent with empirical data on gender-specific prevalence or male-to-female ratios in prevalence-to-notification ratios. This is likely a result of IHME underestimating gender disparity in disease incidence in Viet Nam. While WHO estimates that incidence is over four times higher in men than in women, IHME estimates that

incidence in men is only 50% higher than in women. In contrast, in Malawi, where both WHO and IHME estimate that incidence among men is approximately twice that among women, posterior estimates were consistent with empirical data on gender-specific prevalence and case notification rates, as well as male-to-female ratios in prevalence-to-notification ratios (Web Table 24).

Final sensitivity analyses assumed self-reports of symptom duration prior to treatment accurately described untreated disease duration and examined the impact of this assumption on disease burden estimates. Posterior prevalence estimates from these analyses were only 4 to 12 percent those reported in recent prevalence surveys (for example, 13 (95% CrI: 12, 15) per 100,000 men in Viet Nam) and male-to-female ratios in prevalence-to-notification ratios significantly less than one (Web Table 25). These results illustrate how unlikely it is that self-reports of symptom duration are accurate measures of untreated disease duration in light of recent prevalence surveys.

## DISCUSSION

Our results imply that the substantial gender differences in the epidemiological burden of tuberculosis are almost solely attributable to gender differences in disease incidence and treatment initiation rates, both of which disadvantage men. Although differences between self-reported symptom duration prior to treatment and our model posteriors indicate that both men and women face long periods of undiagnosed tuberculosis disease prior to treatment, men face substantially longer durations of untreated disease. Improved access to tuberculosis diagnostic and treatment services is needed for all individuals, but with more pressing need to better understand and address men's barriers to care.

Our model confirms gender differences in tuberculosis incidence that have already been acknowledged to some extent in estimates from WHO (17) and IHME (31). Men's higher incidence of disease may be a result of a number of factors including biological susceptibility (32, 33), social contact patterns (34, 35), tobacco smoking (36), alcohol consumption (37) and/or undiagnosed or untreated HIV infection (38, 39). While the relative contribution of these different factors is not well-understood, it is clear that there are more new cases of tuberculosis among men than women in both Viet Nam and Malawi, and likely other countries where similar gender differences in prevalence are found (3).

We also found that prevalence and case notification data are simply not consistent with a longer untreated disease duration in women than in men, despite the widespread recognition of women as a key population with need for improved access to tuberculosis services (6-8). Our results imply that men either have lower symptom awareness or face greater barriers in accessing tuberculosis care than women. Men tend to present with more advanced disease and show lower health utilization for tuberculosis (40), like many infectious and non-infectious conditions (38, 39, 41, 42). Men's healthcare decisions are rooted in societal constructs of masculinity, including concepts that lead to societal pressure to neglect symptoms in order to be physically strong and to fulfill roles as the leader and provider for their immediate and extended family (43-48).

Although women with tuberculosis may face greater delays in receiving appropriate medical attention after seeking care (40), our findings suggest that, on average, men's delays in seeking healthcare far outweigh any delays women face after seeking care in these two countries.

Timely access to tuberculosis care is essential for successful patient outcomes and for the prevention of transmission, yet current evidence points to considerable delays between the onset of disease and treatment initiation (49-52). Our findings urge caution in the interpretation of self-

reports as a measure of untreated disease duration, as these estimates appear to substantially underestimate time to treatment initiation for both genders. Patients usually report the time from symptom onset to treatment initiation in terms of weeks (49-52), yet our results and those of others (4, 11, 24, 49-54) suggest instead that years pass between the development of disease and treatment initiation. Self-reports may be limited by recall accuracy and different perceptions of disease. They may also fail to capture the full duration of long-term illness characterized by remissions and relapses along a continuum (55) rather than unrelenting progression of symptom severity (10, 55, 56). It is likely that patients report only the duration of the most recent episode of “acute-on-chronic” symptom deterioration that has led directly to care-seeking and diagnosis, rather than the full duration of untreated disease. The marked differences between self-reported time to treatment initiation and our posterior estimates may explain in part why current passive case finding strategies have not been as successful as initially projected, despite global implementation (57).

There are several limitations to the results presented here. The model chosen for this analysis was deliberately simple to clearly define and examine the overall impact of each parameter within the model. As such, results provided here describe median untreated disease duration and do not take into account heterogeneity within the populations of interest. Furthermore, we cannot assess the relative contribution of specific biological and socio-cultural factors to increased disease incidence and untreated disease duration among men. In addition, we have not included any consideration of smear-negative and extra-pulmonary tuberculosis disease, for which untreated disease duration is likely even longer than described here, although it seems unlikely that the gender differences found here would disappear when other disease types are considered.

Our results imply that the substantial gender differences in the epidemiological burden of tuberculosis are almost solely attributable to gender differences in disease incidence and treatment initiation rates, both of which disadvantage men. Our results add weight to the growing body of evidence that men have a higher incidence of tuberculosis disease (17, 31) and also often face longer delays than women in accessing treatment (3-5). Self-reported symptom duration prior to treatment provides a poor proxy for untreated disease duration for both genders, especially for men. In both Viet Nam and Malawi our posterior median estimates suggest that men spent over a year longer than women prior to initiating treatment for tuberculosis disease.

Despite male disadvantage in accessing care and strong evidence that men have a higher epidemiological burden of disease, discussions of gender and tuberculosis tend to focus on and prioritize the needs of women. There is little consideration that men face substantial gendered barriers of their own when accessing tuberculosis diagnosis and treatment. National and international tuberculosis programs need to reconsider gender disparity as a barrier to achieving the ambitious elimination goals set for tuberculosis under the End Tuberculosis Strategy (13) and the Sustainable Development Goals (14), from the perspective of men.

Acknowledging men as a disadvantaged group with limited access to timely diagnosis and treatment is only a first step. The long duration of untreated disease estimated here, particularly among men, implies inadequate coverage of current case finding strategies. Action is needed to ensure that men are not being unduly disadvantaged by the prominent focus on maternal and child health that characterizes primary care in many countries. Steps must be taken to acknowledge and address the ways in which constructions of masculinity add to and interact with health system barriers that affect men's health seeking behaviors. Systematic screening offers an opportunity to expedite diagnosis with less reliance on severe symptoms (58): the consideration

of screening programs predominately aimed at men is supported by our data showing them to be a high prevalence, high incidence sub-group with longer untreated disease duration than women.

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**Table 1. Model Priors, Empirical Data and Model Posteriors for Viet Nam**

| Parameter   | Model priors <sup>a</sup> |            | Empirical data |            | Model posteriors <sup>a</sup> |            |
|---|---------------------------|------------|----------------|------------|-------------------------------|------------|
|   | median                    | 95% CrI    | estimate       | 95% CI     | median                        | 95% CrI    |
| Incidence rate (annual per 100,000 <sup>b</sup> ) |                           |            |                |            |                               |            |
| Male  | 245                       | 192, 312   |                |            | 258                           | 216, 314   |
| Female  | 58                        | 27, 124    |                |            | 67                            | 56, 83     |
| Untreated disease duration (years)                |                           |            |                |            |                               |            |
| Male  | 0.09                      | 0.02, 0.39 |                |            | 2.20                          | 1.65, 2.89 |
| Female  | 0.11                      | 0.03, 0.38 |                |            | 1.01                          | 0.60, 1.59 |
| Self-cure rate (annual)                           |                           |            |                |            |                               |            |
| Male and female                                   | 0.19                      | 0.09, 0.41 |                |            | 0.17                          | 0.09, 0.31 |
| Untreated-TB mortality rate (annual)              |                           |            |                |            |                               |            |
| Male and female                                   | 0.29                      | 0.11, 0.77 |                |            | 0.21                          | 0.10, 0.41 |
| Prevalence (per 100,000 <sup>b</sup> )            |                           |            |                |            |                               |            |
| Male  |                           |            | 351            | 262, 440   | 305                           | 234, 389   |
| Female  |                           |            | 69             | 39, 99     | 48                            | 29, 75     |
| Notification (per 100,000 <sup>b</sup> )          |                           |            |                |            |                               |            |
| Male  |                           |            | 137            | 123, 151   | 138                           | 125, 153   |
| Female  |                           |            | 47             | 42, 52     | 48                            | 43, 53     |
| Prevalence-to-notification ratio                  |                           |            |                |            |                               |            |
| Male-to-female ratio                              |                           |            | 1.75           | 1.21, 2.58 | 2.18                          | 1.28, 3.90 |

CI: confidence interval; CrI: credible interval; TB: tuberculosis; Untreated disease duration: inverse of treatment initiation rate.

<sup>a</sup> All potential scale reduction factors, which equal one at convergence, were between 1.001 and 1.003.

<sup>b</sup> Modelled as proportion but shown as number per 100,000 population.

**Table 2. Model Priors, Empirical Data and Model Posteriors for Malawi**

| Parameter   | Model priors <sup>a</sup> |            | Empirical data |            | Model posteriors <sup>a</sup> |            |
|---|---------------------------|------------|----------------|------------|-------------------------------|------------|
|   | median                    | 95% CrI    | estimate       | 95% CI     | median                        | 95% CrI    |
| Incidence rate (annual per 100,000 <sup>b</sup> ) |                           |            |                |            |                               |            |
| Male  | 354                       | 235, 534   |                |            | 295                           | 218, 410   |
| Female  | 151                       | 57, 402    |                |            | 161                           | 118, 235   |
| Untreated disease duration (years)                |                           |            |                |            |                               |            |
| Male  | 0.22                      | 0.07, 1.03 |                |            | 2.77                          | 1.83, 4.06 |
| Female  | 0.23                      | 0.06, 1.86 |                |            | 1.88                          | 1.17, 2.86 |
| Self-cure rate (annual)                           |                           |            |                |            |                               |            |
| Male and female                                   | 0.19                      | 0.09, 0.41 |                |            | 0.22                          | 0.10, 0.47 |
| Untreated-TB mortality rate (annual)              |                           |            |                |            |                               |            |
| Male and female                                   | 0.30                      | 0.12, 0.78 |                |            | 0.43                          | 0.18, 0.87 |
| Prevalence (per 100,000 <sup>b</sup> )            |                           |            |                |            |                               |            |
| Male  |                           |            | 303            | 176, 431   | 286                           | 191, 413   |
| Female  |                           |            | 149            | 85, 213    | 134                           | 84, 201    |
| Notification (per 100,000 <sup>b</sup> )          |                           |            |                |            |                               |            |
| Male  |                           |            | 102            | 91, 112    | 103                           | 93, 113    |
| Female  |                           |            | 71             | 64, 78     | 71                            | 65, 78     |
| Prevalence-to-notification ratio                  |                           |            |                |            |                               |            |
| Male-to-female ratio                              |                           |            | 1.42           | 0.91, 2.20 | 1.48                          | 0.83, 2.73 |

CI: confidence interval; CrI: credible interval; TB: tuberculosis; Untreated disease duration: inverse of treatment initiation rate.

<sup>a</sup> All potential scale reduction factors, which equal one at convergence, were between 1.001 and 1.003.

<sup>b</sup> Modelled as proportion but shown as number per 100,000 population.

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**Figure 1: Prevalence and Case Notification Rates by Gender in (A) Viet Nam and (B) Malawi** Dark gray bars indicate distributions for men; light gray bars indicate distributions for women. Lines indicate 95% confidence intervals. Male-to-female ratios in prevalence-to-notification ratios: 1.75 (95% credible interval 1.21-2.58) in Viet Nam and 1.41 (95% credible interval 0.91-2.20) in Malawi.

**Figure 2: Model Diagram**  $prev_g$  is the prevalence in gender  $g$ ,  $not_g$  is the case notification rate in gender  $g$ ,  $inc_g$  is the disease incidence rate in gender  $g$ ,  $ti_g$  is the treatment initiation rate (inverse of untreated disease duration) in gender  $g$ ,  $sc$  is the self-cure rate,  $\mu$  is the untreated-tuberculosis mortality rate.

**Figure 3: Density Plots for Prior and Posterior Distributions for Untreated Disease Duration by Gender in (A) Viet Nam and (B) Malawi.** Prior distributions shown as dashed lines, posterior distributions shown as solid lines. Dark gray lines indicate distributions for men; light gray lines indicate distributions for women.