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Gender differentials of pulmonary tuberculosis transmission and reactivation in an endemic area

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Abstract

Background: In most low-income countries, there are twice as many tuberculosis cases reported among men than among women, a difference commonly attributed to biological and epidemiological characteristics as well as socioeconomic and cultural barriers in access to health care. The World Health Organization has encouraged gender-specific comparisons in tuberculosis rates to determine whether women with tuberculosis are less likely than men with tuberculosis to be diagnosed, reported, and treated.
Objective: To identify gender-based differences in pulmonary tuberculosis patients and use this information to improve tuberculosis control efforts.
Methods: We screened persons with more than 2 weeks cough in southern Mexico from March, 1995 to April, 2003. We collected clinical and mycobacteriological information (isolation, identification, drug-susceptibility testing and IS*6110*-based genotyping and spoligotyping) from individuals with bacteriologically confirmed pulmonary tuberculosis. Patients were treated in accordance with official norms and followed to ascertain treatment outcome, retreatment, and vital status.
Results: We enrolled 623 patients with pulmonary tuberculosis; male:female incidence rate ratio for overall, reactivated and recently transmitted disease was 1.58 (95%CI 1.34 -1.86), 1.64 (95%CI 1.36 - 1.98) and 1.41 (95% CI 1.01 - 1.96), respectively. Men were more likely than women to default from treatment (adjusted OR 3.30, 95%CI 1.46-7.43), to be retreated for tuberculosis (HR 3.15, 95% CI 1.38-7.22), and to die from tuberculosis (HR 2.23, 95%CI 1.25-3.99).
Conclusions: Higher rates of transmitted and reactivated disease and poorer treatment outcomes among men are indicators of gender differentials in pulmonary tuberculosis diagnosis and treatment, and suggest specific strategies in endemic settings.

Introduction

Tuberculosis is the leading cause of death from an infectious disease in women worldwide.[1] In most low-income countries, there are twice as many tuberculosis cases reported among men than among women,[2] a difference commonly attributed to biological and epidemiological characteristics [3][4] as well as socioeconomic and cultural barriers in access to health care.[5] The World Health Organization (WHO) has encouraged gender-specific comparisons in tuberculosis rates to determine whether women with tuberculosis are less likely than men with tuberculosis to be diagnosed, reported, and treated.[5]

Since 1995, we have been conducting a population-based prospective study of pulmonary tuberculosis in southern Mexico. According to the 2000 census, women have less literacy, fewer years of formal education, and higher rates of unemployment in the study area. These indicators are comparable to the state and nationwide rates.[6] We detect and screen individuals who report cough (> 2 weeks) and, if they are diagnosed with tuberculosis, refer them to an appropriate health care provider for treatment. In this study, we sought to determine whether there were gender differences in bacteriologically proven pulmonary tuberculosis incidence rates, the percentage of pulmonary tuberculosis cases due to recent transmission versus reactivation of latent infection and the treatment outcomes of bacteriologically proven pulmonary tuberculosis patients.

Methods

Study population and enrollment

The study site and enrollment procedures have been described previously.[7] Briefly, the study area includes 12 municipalities in the Orizaba Health Jurisdiction in Veracruz State, Mexico. The study area is 618.11 km^2 and has 369,235 inhabitants, 14.9% of them in rural communities.[8] The incidence rate of tuberculosis in the state of Veracruz during 2000 (28.0 cases per 100,000 population) was higher than the incidence rate nationwide (15.9 cases per 100,000 population).[9] We performed passive case finding supported by community-based health workers and screened persons who reported coughing for more than 15 days. Collaboration was established with local health and political authorities for recruitment of participants. The register of tuberculosis patients was reviewed periodically to identify patients with pulmonary tuberculosis who might have been missed by recruiters.

Between March 1995 and April 2003, patients with acid fast bacilli (AFB) or *Mycobacterium tuberculosis* in sputa were evaluated using a standardized questionnaire, physical exam, chest radiograph, and HIV test to determine their epidemiological, clinical, and mycobacteriological characteristics. Treatment was provided using the official norms of Mexico's national tuberculosis control program.[10] We performed annual follow-up to ascertain treatment outcome and vital status, as previously described.[11] Deaths were attributed to tuberculosis based on two of the following: death certificate with tuberculosis as the main cause of death; interview with a close caregiver who identified tuberculosis as a probable cause of death; or bacteriologically confirmed tuberculosis at the time of death.[12]

We obtained written informed consent from each individual prior to enrollment. The study was approved by the institutional review boards of the Instituto Nacional de Salud Pública (INSP), the Instituto Nacional de Ciencias Médicas y de la Nutrición "Salvador Zubirán" (INCMNSZ), and Stanford University.

Mycobacteriology and genotyping

We performed Ziehl Neelsen staining, cultures for mycobacteria, species identification, and susceptibility testing, following standardized procedures.[11][13] Genotypic analysis of *M tuberculosis* isolates was performed using a standard insertion sequence IS*6110* restriction fragment length polymorphism (RFLP) technique with a computer-assisted analysis of the patterns (Bioimage AQ-1 analyzer and Molecular Fingerprinting Analyzer, version 2.0) isolates with identical IS*6110* genotype patterns with less than 6 hybridizing bands were also analyzed using spoligotyping as previously described [11][14] Because we were interested in assessing recent or ongoing transmission of *M. tuberculosis* that rapidly progressed to disease, we established a one year period for defining clustering. Cases were considered "clustered" if two or more isolates from different patients were identified within 12 months of each other and had six or more IS*6110* bands in an identical pattern, or < 6 bands with identical IS*6110* RFLP patterns and a spoligotype with the same spacer oligonucleotides. Pulmonary tuberculosis cases with a unique genotype pattern and the first case diagnosed in each cluster likely arose from the reactivation of a latent tuberculosis infection.

Statistical analysis

To determine if women had lesser probability of screening, we compared the proportion of females among screened individuals with the proportion of females among the general populations, as measured by the 2000 census, [15] and the proportion of females providing three sputum samples with the proportion of males.

We estimated the incidence rate of bacteriologically proven pulmonary tuberculosis by gender and by clustered versus unique genotype patterns. The incidence rate of pulmonary tuberculosis cases was calculated using the census data for the population $\geq$ 15 years of age as the denominator.[15] An annual population estimate was extrapolated for non-census years assuming a steady annual growth rate in the geographical study area.

We used bivariate and multivariate analyses to test for gender-based differences in the patients´ sociodemographic, behavioral, and clinical characteristics. We also compared the bacteriologic characteristics of the isolates of *M. tuberculosis*, such as drug susceptibility test results and genotype patterns, from men versus women. To evaluate access to health care, we assessed the severity of symptoms and disease at diagnosis, the distance to health service centers, the time interval that the patient was symptomatic prior to diagnosis, the time elapsed between diagnosis and starting anti-tuberculosis treatment, and the time elapsed between the onset of symptoms and the start of anti-tuberculosis treatment. Using multivariate unconditional logistic regression, we investigated associations between gender and treatment outcome. We used Kaplan Meier curves to assess survivorship by gender and a log-rank test to detect significant differences.[16] We also constructed Cox proportional hazards models to assess the association of gender with time to retreatment and death. Variables were entered into the models according to their statistical significance in the bivariate analysis ($p \leq 0.2$) and their biological relevance, and were retained based on the chi-square test of the log-likelihood ratios. We used STATA 7.0 (College Station, Texas, USA) statistical software for data analysis.[17]

Results

During the eight-year study period, we screened 8,195 persons who reported cough >2 weeks; 55.7% (4,569) were women. The proportion of women who were screened was larger than the proportion of females in the general population, as measured by the 2000 census (55.7% (n = 4,569 women screened) versus 47.7% (n = 176,120 females), $p< 0.0001$). Age distribution of the group who presented with cough was similar to the general population. Eighty-six percent

of all coughers provided three sputum samples, the proportion of women who provided three samples (86.4% (n = 3,948) versus 84.6% (n = 3,067), p = 0.03) was also slightly greater than the proportion of men. Of all individuals who were screened, 10.1% (829) had AFB or *M. tuberculosis* in at least one sputum sample, and were diagnosed with pulmonary tuberculosis.

We obtained mycobacteriological culture and genotyping results for 75.1% (623/829) of the tuberculosis patients. Patients with a *M. tuberculosis* genotype result available were more likely to have more than 10 bacilli per oil immersion field in the sputum smear (41.25% [257/623] versus 26.2% [54/206], p = 0.001) and severe clinical symptoms such as fever (66.77% [416/623] versus 55.83% [115/206], p = 0.004) or weight loss (75.24% [468/622] versus 67.48% [139/206]), p < 0.05) than tuberculosis patients among whom we were unable to perform genotype study

Incidence rates and incidence rate ratio, by gender.

Of the 623 pulmonary tuberculosis patients, 41.1% (256) were women. Overall, the incidence rate of pulmonary tuberculosis was 58% higher among men (31.79 cases per 100 000 person/years) than women (20.13 cases per 100 000 person/years) (p < 0.001). The incidence rates of clustered pulmonary tuberculosis cases among men and women, representing ongoing transmission (7.54 cases versus 5.35 cases per 100,000 person/years) and reactivated cases of tuberculosis (24.25 cases versus.14.78 cases per 100,000 person/years) were also higher among men than among women (p < 0.05 and <0.001, respectively). Mortality due to tuberculosis was higher among men (3.2 per 100,000 person/years) than among women (1.1 per 100,000 person/years), p=0.0003 (Table 1).

Table 1. Incidence and mortality rates of pulmonary tuberculosis by gender in Orizaba, Veracruz, 1995-2003.

Variables	Men Rate* (No. of cases)	Women Rate* (No. of cases)	Men:women Incidence rate ratio (95% CI)	p value
Incidence rates				
Clustered cases†	7.54 (87)	5.35 (68)	1.41 (1.01-1.96)	0.03
Reactivated cases	24.25 (280)	14.78 (188)	1.64 (1.36-1.98)	<0.001
Total cases	31.79 (367)	20.13 (256)	1.58 (1.34-1.86)	<0.001
Mortality rates				
Due to tuberculosis	3.20 (37)	1.10 (15)	2.91 (1.60-5.30)	0.0003
All cause mortality	7.61 (88)	2.20 (30)	3.46 (2.28-5.23)	<0.0001

*Per 100,000 person-years

†Clustering within one year of diagnosis

Characteristics of clusters, by gender

Of the 623 isolates of *M. tuberculosis* with a genotype result, 24.8% (155) were in clusters and 75.1% (468) had a unique genotype. There were 43 different clusters, each with 2-19 isolates; 67% (29) of index cases were male. Clusters with a female index case were not significantly larger (mean 3.8, median 2.5 cases, range 2-9 cases) than clusters initiated by men (mean 3.4, median 2.0 cases, range 2-19 cases, p = 0.5). Similarly, there was no significant difference in the number of secondary cases by gender.

Characteristics of patients, by gender

The characteristics of the study population, by gender, are shown in Table 2. Men were more likely than women to have some formal education and a higher socioeconomic level (as determined indirectly by household characteristics), but they were also more likely to have lived in a shelter, been imprisoned, or to report using alcohol or drugs. Men were also more likely than women to have severe clinical symptoms, such as weight loss and hemoptysis, at diagnosis. However, there was no significant difference between men and women in the distance from their home to the nearest health care service (p=0.24), the median time interval between the onset of symptoms and diagnosis (p=0.46), the median time interval between the onset of symptoms and treatment (p = 0.18), and the median time interval between diagnosis and the start of treatment (p=0.22).

Table 2. Characteristics of pulmonary tuberculosis patients by gender, Orizaba, Veracruz, 1995-2003.

Characteristics	Total	Men n=367§ (58.91%)	Women n=256§ (41.09%)	p value
Age, (Mean [S.D.])	44.3 (17.8)	45.19 (17.3)	43.12 (18.5)	0.15*
Any formal education (No. [%])	505/620 (81.45)	313/365 (85.75)	192/255 (75.29)	0.001
Potable water available within the household (No. [%])	246/606 (40.59)	157/357 (43.98)	89/249 (35.74)	0.04
Distance to nearest health center (meters), (Median [IQR])	691.81 (436.94-1012.05)	686.93 (437.35-980.23)	705.47 (430.94-1211.67)	0.24†
Used alcohol (No. [%])	285 (45.97)	255/365 (69.86)	30/255 (11.76)	<0.001
Used tobacco (No. [%])	169/620 (27.26)	150/365 (41.10)	19/255 (7.45)	<0.001
Used illegal drug (No. [%])	43/620 (6.94)	42/365 (11.51)	1/255 (0.39)	<0.001
Homelessness or residence in shelters (No. [%])	23/619 (3.72)	22/364 (6.04)	1/255 (0.39)	<0.001
Previous imprisonment (No. [%])	168/619 (27.14)	161/365 (44.11)	7/254 (2.76)	<0.001
HIV infection (No. [%])	15/601 (2.50)	10/352 (2.84)	5/249 (2.01)	0.52
Weight loss (No. [%])	522/611 (85.43)	319/361 (88.37)	203/250 (81.20)	0.01
Hemoptysis (No. [%])	205/619 (33.12)	140/364 (38.46)	65/255 (25.49)	0.001
Cavities in chest radiograph (No. [%])	174/521 (33.40)	98/298 (32.89)	76/223 (34.08)	0.77
Infiltrates in chest radiograph (No. [%])	358/531 (67.42)	230/305 (75.41)	128/226 (56.64)	<0.001
Clustered genotype pattern ‡	155/623 (24.88)	87/367 (23.71)	68/256 (26.56)	0.42
Interval between initiation of symptoms and diagnosis, months (Median [IQR])	2.87 (1.70-5.47)	2.90 (1.70-5.57)	2.78 (1.63-5.0)	0.46†
Interval between initiation of symptoms and treatment, months (Median [IQR])	3.37 (2.07-5.97)	3.50 (2.10-6.20)	3.25 (2.02-5.40)	0.18†
Interval between diagnosis and initiation of treatment, months (Median [IQR])	0.20 (0.07-0.43)	0.20 (0.07-0.047)	0.02 (0.07-0.37)	0.22†
M tuberculosis resistant to isoniazid	36/618	19/366	17/252	0.42

and rifampin (No. [%])	(5.83)	(5.19)	(6.75)	
Initiation of treatment less than 10 days after diagnosis (No. [%])	408/576 (70.83)	242/346 (69.94)	166/230 (72.17)	0.56
Directly supervised treatment (No. [%])	551/562 (98.04)	333/339 (98.23)	218/223 (97.76)	0.69
Treatment outcome				
Cure (No. [%])	471/568 (82.92)	273/343 (79.59)	198/225 (88.0)	0.009
Default (No. [%])	52/568 (9.15)	41/343 (11.95)	11/225 (4.89)	0.002
Retreatment during follow up (No. [%])	47/606 (7.10)	36/355 (9.30)	10/251 (3.98)	0.01
Follow up (months), (Mean [S.D.])	40.81 (32.43)	48.33 (33.43)	49.48 (30.98)	0.66*
Death from tuberculosis (No. [%])	52/623 (8.35)	37/367 (10.08)	15/256 (5.86)	0.06

* ANOVA = analysis of variance

† Mann Whitney statistic

‡ Clustering within one year of diagnosis

No. = number, S.D. = standard deviation; IQR = interquartile range; TB = tuberculosis; HIV = human immunodeficiency virus

§ Because there were missing values for the characteristics of some of the tuberculosis patients, several of the numbers below do not sum to the group total.

Treatment outcomes, by gender

Twelve patients refused treatment. Of 568 patients for whom treatment completion could be evaluated, 75.2% (427/568) had initiated treatment within 10 days after diagnosis and 97.0% (551/568) received directly observed therapy (DOTS). The treatment outcomes overall were as follows: cured, 82.9% (471), 73.8% (419) of them with bacteriological confirmation; defaulted, 9.2% (52); failed treatment, 2.8% (16); died during treatment, 3.0% (17); and transferred out of the study area, 2.1% (12). In the bivariate analysis, men were more likely than women to default from treatment (p = 0.004). Controlling for socioeconomic characteristics, radiological lesions, and the mean time interval between diagnosis and treatment in a multivariate logistic regression analysis, men were still more likely than women to default [OR 3.30, 95% C.I. 1.46-7.43, p = 0.004], (Table 3)**.** Patients were followed for a mean of 40.81 months (standard deviation (SD) 32.43 months). The follow up time was similar for men and women (48.33 months versus 49.48 months, respectively (p = 0.66). After completing treatment, men were more likely than women to have a subsequent episode of tuberculosis and to require retreatment (p = 0.01) (Table 2). The Cox adjusted hazards ratios for retreatment, controlling for diabetes and drug resistance, was higher among men than among women [hazards ratio [(HR) 3.15, 95% C.I. 1.38-7.22, p = 0.007] (Table 3)**.**

Table 3. Results of the multivariate analysis of the risk factors for default, retreatment, and death from tuberculosis among bacteriologically confirmed pulmonary tuberculosis patients, Orizaba Veracruz, 1995 - 2003.

Characteristic	Default		Retreatment		Death from tuberculosis	
	OR* (95% CI)	p-value	HR† (95% CI)	p-value	HR† (95% CI)	p-value
Men	3.30 (1.46-7.43)	0.004	3.15 (1.38-7.22)	0.007	2.23 (1.25-3.99)	0.007
Age (years)	--	--	--	--	1.04 (1.02-1.05)	<0.001
Without any formal education	3.85 (1.85-8.33)	<0.001	--	--	--	--
Lack of social security	4.54 (1.64-12.5)	0.003	--	--	--	--
Body mass index	--	--	--	--	2.28 (1.38-3.79)	0.001
Weight loss	--	--	--	--	2.40 (1.02-5.63)	0.04
Diabetes	--	--	1.83 (0.94-3.54)	0.073	--	--
HIV infection	--	--	--	--	24.30 (9.0-65.6)	<0.001
MDR TB	--	--	4.96 (1.99-12.36)	0.001	2.84 (1.25-6.40)	0.01
Other resistance	--	--	1.33 (0.57-3.10)	0.52	0.7 (0.34-1.43)	0.3
Cavities in chest radiograph	3.70 (1.81-7.58)	<0.001	--	--	--	--
Time interval between diagnosis and treatment (months)	1.02 (1.01-1.04)	<0.001	--	--	--	--
Treatment default	--	--	--	--	5.21 (3.06-8.87)	<0.001

* Based on logistic regression analysis: † Based on a Cox proportional hazard model
OR = odds ratio; HR = hazards ratio; MDR = multidrug-resistant; TB = tuberculosis
-- Variable not included in the final model.

There were 118 tuberculosis patients who died during the study period and death was due to tuberculosis in 52 of 118 instances (44.07%). Of these 52 patients; three untreated patients, 17 patients during treatment, and 32 patients after treatment died from tuberculosis. Four of the twelve patients who refused treatment, all of them men, died. The Cox adjusted hazards ratios for mortality from tuberculosis controlling for age, body mass index, weight loss, HIV infection, drug resistance and treatment default, was higher among men than among women [hazards ratio [(HR) 2.23, 95% C.I. 1.25-3.99, p = 0.007] (Table 3**).** Male patients had lower survival rates when death due to tuberculosis p=0.05 (Figure 1A) from other causes, p = 0.02 (Figure 1B) and death from all causes, p=0.004 (Figure 1C), were assessed.

Since alcohol usage was more frequent among men, we evaluated models that included alcohol as an independent variable. Men were more likely to default, require retreatment or die from tuberculosis when models were also adjusted by usage of alcohol.

Discussion

In this population based study conducted in a developing country with endemic rates of tuberculosis, we provide data indicating higher rates of bacteriologically proven pulmonary tuberculosis and more severe clinical consequences among men as compared to women. By using molecular epidemiologic techniques, we further determined that higher rates among men are the result of both reactivation of latent infection and of recent tuberculosis transmission. Public health strategies that aim to reduce tuberculosis will need to address both disease processes, reactivation of latent infection and recent or ongoing transmission.

Data indicating higher tuberculosis rates for men, particularly when obtained from developing countries [18][19] have been highly controversial and have often been attributed to gender-based differences in access to health care.[20] Existing evidence indicates that the access to and use of health care services in Mexico is similar across genders, and in fact, women use the health services more frequently than men.[21] Although the female patients in our study came from lower socioeconomic groups than the male patients, these differences did not represent an obstacle for pulmonary tuberculosis screening, diagnosis, and treatment in the study area since such services are available free of charge through the public health sector in Mexico. In our study, the proportion of women who reported coughing for at least two weeks, provided sputum samples, and were screened for tuberculosis was greater than the proportion of men who were screened. There were no significant gender-based differences in the distance to the nearest health center, and in the time interval between the onset of symptoms and the start of anti-tuberculosis treatment. Although the median time intervals to diagnosis and treatment were similar between genders, men had more severe clinical symptoms at the time of diagnosis than women. It is possible that symptoms such as coughing might have initially been attributed to other causes such as tobacco use, and therefore men were symptomatic for longer intervals before seeking care. We consider that the higher rates of pulmonary tuberculosis among men that we detected are not attributable to unequal access to health services for diagnosis and treatment. A recent study in south India also reported that women were more likely than men to access the health care services.[22]

Differences in tuberculosis rates have also been attributed to biological phenomena. It has been suggested that the propensity to develop disease after infection with *M. tuberculosis* (progression rate) may be greater among women of reproductive age than among men of the same age, whereas men have higher rates of progression at older ages [23][24]. Comorbid conditions, such as human immunodeficiency (HIV) infection,[25] diabetes,[26] and cirrhosis,

[27] could also affect the rate at which tuberculosis occurs, and their prevalence could vary by gender. We also note that men not only had higher rates of pulmonary tuberculosis, but also had more severe clinical symptoms when diagnosed with tuberculosis.

The higher rates of pulmonary tuberculosis among the men in our study are partially explained by the local transmission dynamics, particularly in crowded, poorly ventilated or nosocomial settings. Men are more likely to report risk factors that have been associated with exposure to tuberculosis,[28] such as imprisonment [29] or prior residence in a shelter.[30] We previously described an outbreak of tuberculosis in the study area that was occurring in clandestine bars, whose customers were mainly men.[7] Men also reported more frequent use of alcohol and tobacco, behaviors that may influence the rate at which a tuberculosis infection progresses to active disease.[31][32] Evaluation of male gender and alcohol, using logistic regression analyses and Cox models, demonstrated that men with tuberculosis are at a higher risk of a poor treatment outcome, independently of alcohol use.

There were significant differences in the outcomes of anti-tuberculosis treatment between men and women. Although women were just as likely as men to be treated with directly observed therapy, men were more likely to default from treatment. The behaviors of non-adherent male patients have been amply described.[33][34] Most likely because of defaulting from treatment, men were more likely than women to require retreatment, as has been reported.[35] Finally, the probability of death due to tuberculosis among men more than doubled that of women adjusting by variables which we have observed to be associated to mortality in this setting such as drug resistance and HIV infection.[12] In fact, male patients also had a higher probability of death due to other causes and of death due to all causes. This higher probability of death due to tuberculosis among men has been confirmed elsewhere.[36]

The inferences that can be drawn from our study are limited by several potential biases. Determining the cause of death can be a complex process. In this study, we used a combination of criteria (clinical, bacteriological and caregiver interview, and/or death certificate) to ascertain cause of death,[2][37] which allowed us to estimate mortality rates. We have validated this method previously.[12] The cause of death profile derived from interview of a close caregiver or verbal autopsy has also been demonstrated to be useful by other authors.[37] It should be noted that we studied only bacteriologically proven pulmonary tuberculosis cases. Our data may not be generalizable to patients with scantier bacilli and less severe symptomatology since our study population differed in bacilli concentrations and clinical manifestations from the total pulmonary tuberculosis cases. Finally, we only explored epidemiological and clinical information; other sociological and behavioral aspects which might determine gender differentials were not included in our study. Nevertheless, our population based study allowed us to calculate unbiased pulmonary tuberculosis rates for men and women regardless of the complexity of other factors that were not considered.

The present study documented gender differentials in the incidence rates of bacteriologically proven pulmonary tuberculosis, which reflect both reactivation of a latent tuberculosis infection and recent transmission of *M. tuberculosis* and which are not likely to be explained by differential access to health care services in Mexico. We also report gender differentials in treatment outcomes, with males having poorer outcomes than women. Our data support the need to devise and implement tuberculosis control strategies to block further tuberculosis transmission, including better case finding and assurances that each tuberculosis patient is cured. Our data also show that increased screening and treatment of latent infection will be needed to decrease the incidence of reactivated disease.

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Competing interest statement

All authors declare have not relevant competing interests.

Figure 1. Kaplan Meier survival curves by gender, (A) Death from tuberculosis (p=0.05), (B) Death by some cause other than tuberculosis (p=0.02), and (C) Death from all causes (p=0.004). Estimated survival of bacteriologically confirmed pulmonary tuberculosis patients according to gender. Male patients had lower survival rates when death from tuberculosis was analyzed (Panel A, p=0.05); death from other causes (Panel B, p=0.02) and death from all causes (Panel C, p=0.004) were analyzed.

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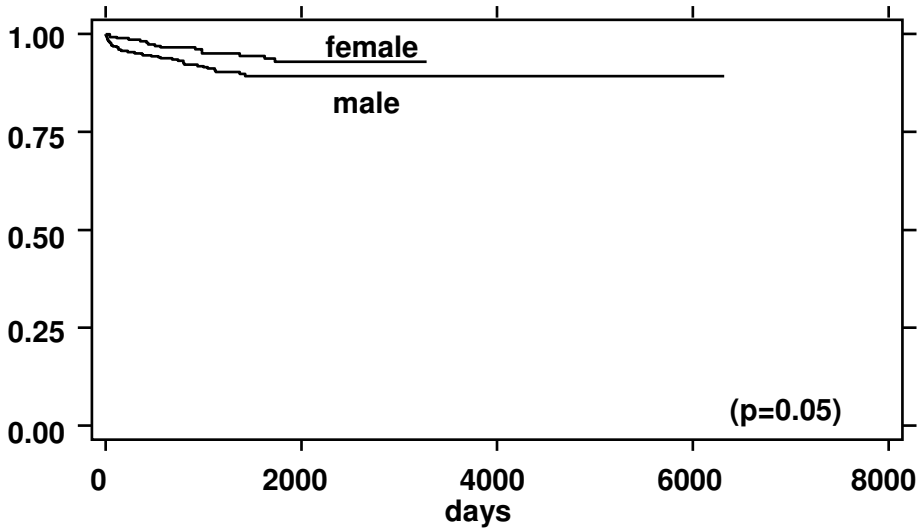
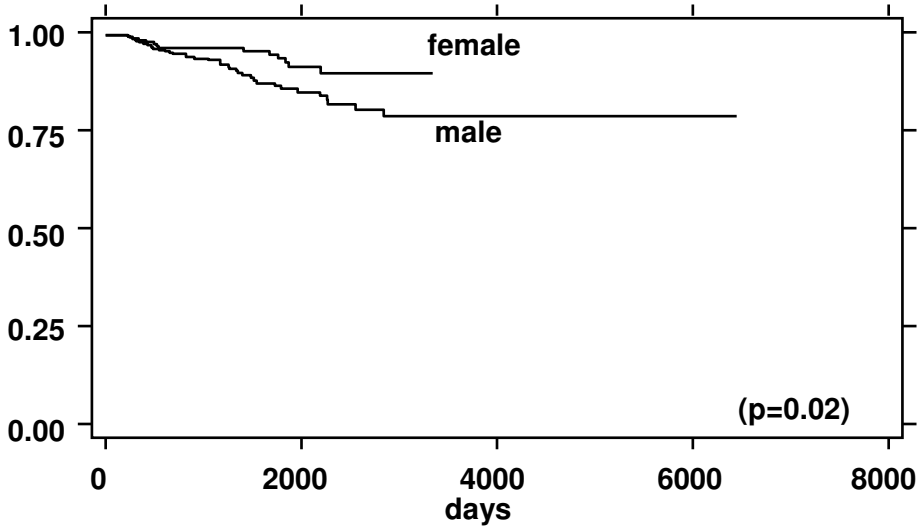
Figure 1. (A) Death from tuberculosis



(B) Death by some cause other than tuberculosis



(C) Death for all causes