ELSEVIER

Journal of Clinical Epidemiology 55 (2002) 115–120

Journal of Clinical Epidemiology

Difference in symptoms suggesting pulmonary tuberculosis among men and women

Nguyen Hoang Long[a,b,c,*], Vinod K. Diwan[c,d], Anna Winkvist[d]

[a]*National Institute of Tuberculosis and Respiratory Diseases, 463 Hoang Hoa Tham Street, Hanoi, Vietnam*
[b]*Division of Epidemiology, Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden*
[c]*Division of International Health (IHCAR), Department of Public Health Sciences, Karolinska Institutet, Stockholm, Sweden*
[d]*The Nordic School of Public Health, Göteborg, Sweden*

Received 5 November 2000; received in revised form 27 July 2001; accepted 16 August 2001

Abstract

Longer delays in diagnosis and lower case-detection of tuberculosis (TB) among women remain a problem in many countries. This study describes reported symptoms of new smear-positive pulmonary TB among men and women, and their association with TB diagnostic delays. All 1,027 new smear-positive pulmonary TB cases aged 15 years or over (757 men and 270 women) diagnosed by 23 district TB units of four provinces in Vietnam during 1996 were interviewed at the time of diagnosis. Among these, 540 patients diagnosed during January–June 1996 were followed up during treatment course. Pattern of symptoms was similar between the sexes. However, symptoms of cough (90.7% women, 94.7% men, P = .021), sputum expectoration (83.6% women, 89.9% men, P = .006), and hemoptysis (27.8% women, 34.9% men, P = .033) were less common among women than among men. Absence of cough and sputum expectoration was significantly associated with increased doctor's delays. Two months after treatment, cough and sputum expectoration recovered significantly more quickly among women compared to men.

Keywords: Tuberculosis; Clinical symptoms; Delays; Sex; Vietnam

1. Background

In our earlier study of a cohort of 757 male and 270 female smear-positive pulmonary tuberculosis (TB) cases, we reported that total delay from onset of symptoms to diagnosis of the disease was significantly longer among women than among men. This gender difference in delay was mainly due to longer doctor's delay in women (mean 5.4 weeks) compared to men (mean 3.8 weeks) [1]. A number of studies have reported long delays to TB diagnosis due to both patient's delay in seeking care and health care worker's delay in making TB diagnosis [2,3]. However, only a few studies have addressed gender differences in delays in seeking health care, and to our knowledge, none has reported the underlying reasons for the difference in delay among men and women.

The question of delays in seeking health care and receiving diagnosis is important in the context that in most low- and middle-income countries, around two-thirds of notified TB cases are men and only one-third are women [4]. It is unclear why more men than women are diagnosed with TB [5]. Notification data from some European countries at the time when TB incidence and prevalence were high showed a different pattern among men and women. More women were reported to be suffering from TB, particularly in the age of 20–34 years compared to the men in the same age group [6]. Some hypotheses have been proposed with regard to differences in reported TB cases among men and women in developing countries. These include higher exposure to infection among men (after 15 years of age) leading to higher incidence of TB and under diagnosis and notification among women (due to socio-cultural and economic reasons) [7]. Differences in clinical symptoms of the disease between men and women may lead to different level of suspicion of TB for men and women and eventual differences in the rate of investigation and diagnosis of the disease.

Vietnam is one of the few developing countries with a good TB control program. According to WHO TB Control, Vietnam is one of the few countries among the top 22 high TB burden countries to have reached TB control targets of WHO. High treatment success rates have been maintained at around 90%, and case detection in 1997 was 77% of estimated smear-positive incidence [8]. Similar to

* Corresponding author. Tel.: +84.4 8231440; fax: 84.4 8463056.
E-mail address: longmoh@yahoo.com (N.H. Long)

0895-4356/02/$ – see front matter
PII: S0895-4356(01)00455-3

many other developing countries, in Vietnam also, about two-thirds of the detected cases are men and only one-third are women [9].

The aim of this article is to describe and compare clinical symptoms of new smear-positive pulmonary TB among men and women, how these symptoms influence TB diagnostic delays, and estimate the rate of improvements in clinical symptoms for both sexes.

2. Method

This study was conducted in four provinces (Hanoi, Quang Ninh, Ho Chi Minh City, and Quang Nam-Da Nang) purposively selected from different regions of Vietnam (e.g., north and south, urban and rural areas). A sample of 23 districts was randomly selected from a total of 56 districts in these four provinces using stratified sampling technique with respect to geographic areas and number of TB patients detected in 1995. All 1,027 new smear-positive pulmonary TB cases aged 15–49 years diagnosed from 1 January to 31 December 1996 by the district TB units (DTUs) of these 23 districts were included in the study. No refusals or missed cases were reported.

In each district, there is a DTU and about 5–10 hospital beds reserved for TB in-patients in the district general hospital. Tuberculosis suspects could primarily be identified by commune health workers and then referred to the district hospital, or they could go directly to the hospital for medical examination. As a routine practice of the National TB Control Programme in Vietnam, district hospitals and DTUs diagnose smear-positive pulmonary TB cases using direct microscopy examination. Smear-negative pulmonary and extrapulmonary TB cases are diagnosed by provincial TB centers. After diagnosis, most smear-positive pulmonary TB cases are treated by the DTU [10].

A total of 23 health professionals (22 doctors and 1 assistant doctor) in charge of the selected DTUs were recruited and trained for data collection. The patients were interviewed using a structured questionnaire just after the confirmation of the TB diagnosis. Using a structured symptom list, interviewers asked the patient for each clinical symptom. Data on geographic, socio-economic and demographic variables, and health care seeking behavior were also collected. Economic class of the patients was identified according to the number of valuable items in their households, for example, bicycle, radio, cassette, refrigerator, TV, video, telephone, motorcycle, etc. Four economic levels were classified: very poor (no items), poor (one to two items), average (three to six items), and rich (7–10 items).

Out of 1,027 patients mentioned above, 540 patients diagnosed during January–June 1996 were selected for follow-up of improvements in clinical symptoms and sputum examination 2, 5, and 8 months after start of treatment (for patients taking 8-month regimens) or 2, 4, and 6 months (for patients taking 6-month regimens). This follow-up was conducted within the routine procedure of the TB control program in Vietnam.

Data entry, descriptive statistics, and bivariate analyses were performed using Epi-Info 6.04. Chi-square tests and *t*-tests were used to compare men and women with regard to prevalence of symptoms and mean delays. To control for confounding factors, multiple linear regression analyses were performed. Symptoms of cough, sputum expectoration, and hemoptysis were entered in the regression models as dependent variables. Sex, age, family size, number of valuable items, and area of residence (urban or rural) were included in the models as independent variables. Statements about statistical significance refer to $P < .05$ unless otherwise stated.

3. Results

3.1. Background information

A total of 1,027 patients aged 15–49 years (757 men and 270 women) with new smear-positive pulmonary TB were interviewed. Within 15–49 years of age, the mean age of getting TB was found to be significantly lower for women compared to men, 32.7 years and 34.2 years, respectively. Educational level was significantly higher in men than in women. No significant difference was noted

Table 1
Information on demographic and socio-economic variables of 757 men and 270 women with new sputum smear-positive pulmonary TB

	Men ($N = 757$)		Women ($N = 270$)	
Variable	*n*	%	*n*	%
Age group (in years)				
15–19	21	2.8	16	5.9
20–24	74	9.8	43	15.9
25–29	132	17.4	44	16.3
30–34	146	19.3	53	19.6
35–39	167	22.1	48	17.8
40–44	134	17.7	29	10.7
45–49	83	11.0	37	13.7
Educational level				
Illiterate	19	2.5	9	3.3
Primary education	78	10.3	38	14.1
Secondary education	236	31.2	103	38.1
High school education or higher[a]	424	56.1	120	44.4
Area of residence				
Urban	248	32.8	98	36.3
Rural	509	67.2	172	63.7
Family size				
1–3 members	122	16.2	61	22.6
4–5 members	324	42.8	104	38.5
6 or more members	311	41.1	105	38.9
Economic class				
Very poor	61	8.1	29	10.7
Poor	275	36.3	99	36.7
Average	411	54.3	136	50.4
Rich	10	1.3	6	2.3

[a]P-value = .001.

between men and women in area of residence and family size (Table 1).

3.2. Reported symptoms at diagnosis

General symptoms (e.g., fever, tiredness, anorexia, headache) were significantly more common in women than in men. Although the differences between men and women were small, reported symptoms of cough, sputum expectoration, and hemoptysis were statistically significantly less common in women than in men (Table 2). Multiple linear regression analysis showed that the differences between men and women with regard to prevalence of cough, sputum expectoration, and hemoptysis remained significant after controlling for age, family size, housing condition, and area of residence. A combination of five most common symptoms in men included cough, sputum expectoration, weight loss, fever, and tiredness. Women had the same combination of symptoms, but in a different order, i.e., cough, sputum expectoration, tiredness, fever, and weight loss.

In an earlier study [1], we reported that mean doctor's delay was significantly longer for women than for men. In the present study, we examined to what extent symptoms reported by men and women could explain delays in diagnosis. Multiple linear regression analyses showed that presence of cough and sputum expectoration was significantly associated with reduction of doctor's delay by 4.13 and 2.13 weeks, respectively, when both men and women were put into analysis together. Other factors (being woman, having fewer valuable items in the family, and living in rural areas) also significantly increased doctor's delay (Table 3).

Regression analyses, with doctor's delay as the dependent variable, were run separately for men and women. The results indicated that absence of cough was significantly associated with an increase of doctor's delay by 4.77 weeks (95%CI 0.40, 9.13) among women and 3.00 weeks (95%CI 0.53, 5.40) among men. Absence of sputum expectoration was associated with an increase of doctor's delay by 2.54 weeks (95%CI 0.27, 4.77) among women and 1.84 weeks (95%CI 0.18, 3.50) among men. Although the increase in doctor's delay was larger among women than among men, this difference between men and women was not statistically significant.

Table 2
Reported symptoms at diagnosis of new smear-positive pulmonary TB by sex

	Men		Women			
Symptoms	*n*	%	*n*	%	Chi-square	P-value
Cough	712	94.7	244	90.7	5.25	.021
Sputum expectoration	669	89.9	224	83.6	7.63	.006
Weight loss	558	73.7	205	75.9	0.51	.475
Fever	530	70.0	206	76.3	3.87	.049
Tiredness	522	69.0	212	78.5	8.92	.003
Anorexia	402	53.1	178	65.9	13.31	.000
Chest pain	441	58.3	140	51.9	3.32	.068
Hemoptysis	264	34.9	75	27.8	4.53	.033
Headache	150	19.8	74	27.4	6.73	.009

Table 3
Relation between doctor's delay (in weeks) and symptoms and socio-economic variables in multiple linear regression analysis

	Change of doctor's delay (in weeks)	95%CI		
Independent variables		Lower	Upper	P-value
Cough	−4.13	−6.29	−1.98	.005
Sputum expectoration	−2.13	−3.83	−0.42	.025
Hemoptysis	−0.13	−1.13	0.88	>.05
Age	0.05	−0.01	0.11	>.05
Sex	−1.19	−2.27	−0.12	.049
Valuable item	−0.31	−0.59	−0.04	.025
Resident area	−1.73	−2.76	−0.70	.005
Family size	0.09	−0.10	0.29	>.05

Symptoms: yes = 1, no = 0; Age: in year; Sex: female = 1, male = 2; Valuable item: Number of valuable items of the household; Resident area: rural = 1, urban = 2; Family size: Number of household members.

The number of symptoms was compared between men and women. Bivariate analyses showed that the mean number of symptoms was significantly higher in women than in men (5.3 and 5.0 symptoms, respectively, P-value = 0.04). However, after controlling for confounding variables, for example, age, family size, housing condition, and area of residence, the difference was no longer statistically significant.

3.3. Follow-up during treatment course

A total of 540 new smear-positive pulmonary TB patients were followed up during their treatment course. Three follow-up visits were done with 444 patients (143 women and 301 men) that allowed comparing progress along the whole treatment course. Among these, about 90% of both male and female patients were treated by Directly Observed Therapy short-course regimen—DOTS—(2SRHZ/6HE: 2 months of intensive treatment with Streptomycin, Isoniazid, Rifampicin, and Pyrazinamide, followed by 6 months of continuation treatment with Ethambutol and Isoniazid). Four symptoms (cough, sputum expectoration, hemoptysis, and fever) were followed up and compared between treatment periods and between men and women. After 2 months of treatment most of the symptoms disappeared. Symptoms of cough and sputum expectoration were significantly more quickly recovered in women than in men ($P < .05$). This difference remained significant after controlling for age, treatment regimen, and place of treatment. For other symptoms, there was a general trend that recovery rates were higher in women than in men, but not significantly different. Although a few male patients remained smear-positive in the later treatment periods, sputum conversion was not significantly different between men and women throughout treatment course (Table 4). Data for those patients who had either one follow-up visit (23 patients) or two follow-up visits (63 patients) were also included in the analysis. However, this did not change the statistical significance of the findings reported above.

Table 4
Symptom recovery and sputum conversion rates (%) by treatment period

Symptoms		No. of patients with symptom/ finding at the time of diagnosis	Number and percentage of patients with symptom disappeared and finding improved		
			Follow-up 1 after 2 months	Follow-up 2 after 4 or 5 months	Follow-up 3 after 6 or 8 months
Cough	Women	142	58 (40.8%)	88 (62.0%)	125 (88.0%)
	Men	292	81 (27.7%)	196 (67.1%)	258 (88.4%)
	P-value	—	0.006	0.289	0.920
Sputum expectoration	Women	136	67 (49.3%)	104 (76.5%)	131 (96.3%)
	Men	287	111 (38.7%)	220 (76.7%)	271 (94.4%)
	P-value	—	0.039	0.967	0.401
Fever	Women	90	88 (97.8%)	90 (100.0%)	90 (100.0%)
	Men	182	174 (95.6%)	182 (100.0%)	182 (100.0%)
	P-value	—	0.579	—	—
Hemoptysis	Women	40	38 (95.0%)	40 (100.0%)	40 (100.0%)
	Men	97	82 (84.5%)	93 (95.9%)	96 (99.0%)
	P-value	—	0.160	0.456	—
Sputum conversion	Women	143	139 (97.2%)	143 (100.0%)	143 (100.0%)
	Men	301	285 (94.7%)	297 (98.7%)	298 (99.0%)
	P-value	—	0.232	0.397	—

4. Discussion

From this study, symptoms suggesting pulmonary TB (e.g., cough, sputum expectoration, and hemoptysis) were significantly less frequently reported by women than by men with new smear-positive pulmonary TB. The absence of cough or sputum expectoration is significantly associated with increased doctor's delay. The difference between men and women in above reported symptoms can be explained by both biological and socio-cultural factors. Biologically, respiratory symptoms reflect lesions in lungs, and symptoms and signs become more prominent with progressive pulmonary involvement [11]. A study from Japan suggests that the stage and the extent of lung lesions be less advanced among female than among male TB patients [12]. This difference may cause lower frequencies of the above respiratory symptoms in women. Although very little empirical data is available on different symptoms among male and female TB patients, there are suggestions that men have stronger hypersensitivity to Mycobacterium [13], as indicated by the tuberculin reaction [14,15]. Furthermore, the X-chromosome holds a number of important genes that could have a bearing on the pathogenesis of infectious TB [13]. Culturally, coughing, hawking, and spitting sputum in general are less acceptable for women than for men; therefore, women may less report these symptoms. In general health care, studies have shown that women more often than men report symptoms and take medication [16,17].

The difference between sexes in reported symptoms is clinically small, but statistically significant, and it partly explains the longer doctor's delay among women. In this study, we cannot explain if the difference in symptoms is due to biological or socio-cultural factors. However, our findings suggest an area for further research and investigation.

Following the recommendation of the World Health Organization (WHO) and International Union Against Tuberculosis and Lung Disease (IUATLD), TB control program in Vietnam has routinely applied passive-case finding approach with highest priority given to detecting and treating smear-positive pulmonary TB [10]. The most important symptom suggestive of pulmonary TB, as proposed by the TB control program, is a cough persisting for more than 3 weeks. A person with a cough of this duration should be tested for Acid Fast Bacilli (AFB) in the sputum using the Ziehl-Neelsen technique with direct microscopy. Therefore, symptoms of cough and sputum expectoration play very important role in detecting smear-positive pulmonary TB cases.

For successful control of TB and reduction of incidence, early diagnosis and adequate treatment play an important role. Unnecessary delay in diagnosis needs to be eliminated or reduced. On the part of health care, this will mean high suspicion for TB among health care seekers. Longer doctor's delay among women reported in our earlier study [1] could be partly explained from the present study. Cough is considered to be the most important symptom suggesting pulmonary TB, and was less common in women than in men. This may lead to doctors not suspecting TB in women. Sputum expectoration was also significantly less common in women than in men. This again may lead to low suspicion and/or low quantity and quality of sputum from women, thus low probability of finding a positive result. Furthermore, a population-based study in Vietnam reported that among people with a cough of more than 3 weeks seeking care from hospitals, significantly fewer women than men were reportedly requested a sputum test [18].

According to Vietnamese tradition, hawking and spitting sputum are less acceptable for women than for men. This

may be a barrier for women to produce a good quality sputum specimen, leading to lower possibility in finding AFB in sputum specimens. In addition, information suggests that more commonly than men, women do not come back to the DTU in the second day when they are requested to bring the second sputum specimen taken at home. This may be because women are busy with children, housework, and dependent on the husband and in-laws. These factors need further investigation.

A study in Japan reported that culture-positive rate and the amount of bacilli on smear were lower in women than in men. The authors suggested that it might be due to the fact that stage and extent of lesions on the lungs were less advanced in women than in men, as mentioned earlier [12].

After 2 months of treatment, recovery from cough and sputum expectoration was significantly quicker among women than men. About 90% of both male and females patients were treated by DOTS with the intensive treatment phase for first 2 months. During these 2 months, treatment is strictly observed by the health care providers, thus noncompliance during first 2 months is considered minimal. The study in Japan also reported that most patients converted to bacilli negative within 3 months after the initiation of the chemotherapy, but few male patients still remained positive [12]. This could be due to the fact that the stage and extension of lung lesions were more advanced among men than women [12]. In addition, women were perceived to be more compliant than men in the TB treatment [19]. Furthermore, men may deny or ignore their disease manifestation longer than women, leading to more advanced disease among men at the time of treatment initiation.

This study was carried out at the district TB units, the basic and the key level of TB control program in Vietnam. We included only new sputum smear-positive pulmonary TB cases for which diagnostic criteria are standardized, and routinely applied by trained DTU staff. Therefore, the probability of misclassification is minimal. A large population in different parts of Vietnam was covered by the study, and we believe that the study population well represents new smear-positive pulmonary TB patients managed by the TB program. However, the TB control program routinely recruits only people who voluntarily present themselves to the DTUs (passive case-finding). Therefore, we have no information about people with TB who did not seek health care, or people who sought care at other health care providers (e.g., private sectors) and not the DTUs. However, with the high coverage of the TB control program (95% of Vietnam population), high DOTS coverage (90% of the detected patients) and high case-detection rate at about 70% of estimated cases [20], the majority of smear-positive pulmonary TB cases are expected to be managed by the DTUs.

As only patients diagnosed with new smear-positive TB were interviewed, the findings from this study may not be generalized to the patients with possible pulmonary TB in the general outpatient departments. However, the absence of key symptoms of pulmonary TB significantly increased doctor's delay in TB diagnosis, we would expect that the frequency of symptoms between male and female outpatients seeking general or TB care could also differ considerably.

At the district level, paramedical parameters (e.g., blood tests) were not routinely performed for TB cases; thus, they were not included in the study. Other clinical signs (e.g., auscultation findings) were not included because of low reliability. As information on smoking was not collected in this study, we could not control for it as a confounder. In an on-going study, we are analyzing chest X-ray findings for sputum positive male and female pulmonary TB patients. This will be reported separately.

In conclusion, a general trend of symptoms of pulmonary TB reported by new sputum smear-positive pulmonary TB patients was similar between men and women. However, key symptoms suggesting TB, for example, cough, sputum production, and hemoptysis, were significantly less common among women than among men. Absence of cough and sputum expectoration was significantly associated with increased doctor's delay. The findings of this study may help to improve TB diagnosis among women in Vietnam.

Acknowledgments

We highly appreciate the assistance in statistical analysis rendered by Bo Eriksson from the Nordic School of Public Health, Göteborg, Sweden. Support for the study presented in this article has been gratefully received in the form of grants from Sida/SAREC, Karolinska Institutet, and Vårdalstiftelsen, Sweden.

References

[1] Long NH, Johansson E, Winkvist A, Diwan V. Longer delays in tuberculosis diagnosis among women in Vietnam. Int J Tuberc Lung Dis 1999;3(5):388–93.
[2] Mori T, Shimao T, Jin BW, Kim SJ. Analysis of case-finding process of tuberculosis in Korea. Tuber Lung Dis 1992;73:225–31.
[3] Hooi LN. Case-finding for pulmonary tuberculosis in Penang. Med J Malaysia 1994;49:223–30.
[4] Kumaresan JA, Raviglione MC, Murray CJL. Tuberculosis. In: Murray CJL, Lopez AD, editors. The global burden of disease and risk factors in 1990. Geneva: World Health Organisation and the World Bank, 1996.
[5] Diwan V, Thorson A. Sex, gender and tuberculosis. Lancet 1999;353 (9157):1000–1.
[6] Holmes CB, Hausler H, Nunn P. A review of sex differences in the epidemiology of tuberculosis. Int J Tuberc Lung Dis 1998;2:96–104.
[7] Diwan VK, Thorson A, Winkvist A, editors. Gender and tuberculosis. Göteborg: The Nordic School of Public Health, NHV Report, 1998. p. 3.
[8] Netto EM, Dye C, Raviglione MC. Global tuberculosis control—WHO Report 1999. Geneva: World Health Organization, 1999.
[9] Vietnam National TB Control Programme. Review of TB control activities in 1997 and Orientations for 1998 for Northern and Central Provinces (in Vietnamese). Hanoi: Vietnam National TB Control Programme, 1998.
[10] Co NV, Duong BD, Duong HS, Thinh PT, Linh NN, Qui NK, Thiep PT. Implementation guidelines for the National TB Control Programme (in Vietnamese). Hanoi: Medical Publishing House, 1999.

[11] Banner AS. Tuberculosis clinical aspects and diagnosis. Arch Intern Med 1979;139:1387–90.
[12] Matsushita Y, Ikeda N, Kurasawa T, Sato A, Nakatani K, Inoue T, Ikeda T, Sakatani M, Kobayashi C, Ozawa S, Kanai K, Suruta N. The characteristics of clinical features of pulmonary tuberculosis in female (in Japanese). Kekkaku 1996;71:391–8.
[13] Bothamley GH. Sex and gender in the pathogenesis of infectious tuberculosis: a perspective from immunology, microbiology and human genetics. In: Diwan VK, Thorson A, Winkvist A, editors. Gender and tuberculosis.. Gothenburg: The Nordic School of Public Health, NHV Report, 1998. p. 41–53.
[14] Kurasawa T. Tuberculin skin tests of patients with active pulmonary tuberculosis and non-tuberculosis pulmonary disease. Kekkaku 1990; 65:47–52.
[15] Shaaben MA, Abdul AM, Bahr GM, Stanford JL, Lockwood DN, McManus IC. Revaccination with BCG: its effects on skin tests in Kuwaiti senior school children. Eur Resp J 1990;3:187–91.
[16] Cecilie MT, van Wijk G, Kolk AM, van den Bosch WJHM, van den Hoogen HJM. Male and female morbidity in general practice: the nature of sex differences. Soc Sci Med 1992;35(5):665–78.
[17] Dean K. Self-care components of lifestyles: the importance of gender, attitudes and the social situation. Soc Sci Med 1989;29(2):137–72.
[18] Thorson A, Hoa NP, Long NH. Health-seeking behaviour of individuals with a cough of more than 3 weeks. Lancet 2000;356(9244):1823–4.
[19] Johansson E, Long NH, Diwan VK, Winkvist A. Attitudes to compliance with tuberculosis treatment among women and men in Vietnam. Int J Tuberc Lung Dis 1999;3(10):862–8.
[20] Vietnam National TB Control Programme. Meeting on 1996–2000 TB control mid-term review and orientation for the coming period (in Vietnamese). Hanoi: Vietnam National TB Control Programme, 1999.