Time from symptom onset to the initiation of treatment of pulmonary tuberculosis in a city with a high incidence of the disease*

Tempo entre o início dos sintomas e o tratamento de tuberculose pulmonar em um município com elevada incidência da doença

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Abstract

Objective: To estimate the time elapsed between the onset of symptoms and the initiation of treatment of pulmonary tuberculosis among treatment-naïve patients with positive results in sputum smear microscopy, and to evaluate the variables associated with delays in diagnosis and in treatment initiation. **Methods:** This was a descriptive exploratory study involving 199 treatment-naïve tuberculosis patients ≥ 12 years of age with AFB-positive sputum smear microscopy results between 2006 and 2008. At their first (treatment initiation) visit to a primary health care clinic in the city of Nova Iguaçu, Brazil, the patients were interviewed and their ancillary test results were reviewed. **Results:** The medians (and respective interquartile ranges) of the time from symptom onset to the initiation of treatment of pulmonary tuberculosis, from symptom onset to seeking medical attention, from entry into care to diagnosis, and from entry into care to treatment initiation, in weeks, were 11 (6-24), 8 (4-20), 2 (1-8), and 1 (1-1), respectively. The variables gender, age, level of education, previous use of antibiotics, HIV status, site of first medical visit, and radiological extent of tuberculosis showed no associations with the time from entry into care to diagnosis or to treatment initiation. The main reason for the delay in seeking medical attention reported by the patients was their inability to recognize their symptoms as indicators of a disease. **Conclusions:** Among the patients studied, there was an unacceptably long delay between the onset of symptoms and the initiation of tuberculosis treatment.

Keywords: Tuberculosis/diagnosis; Tuberculosis/therapy; Delayed diagnosis.

Resumo

Objetivo: Estimar o tempo entre o início dos sintomas e o início do tratamento de pacientes com tuberculose pulmonar virgens de tratamento e com resultado positivo na baciloscopia direta do escarro, assim como avaliar as variáveis associadas à demora no diagnóstico e no início do tratamento. **Métodos:** Estudo descritivo exploratório em pacientes virgens de tratamento para tuberculose, com idade ≥ 12 anos e resultado positivo para BAAR no escarro. Entre 2006 e 2008, os 199 pacientes incluídos no estudo foram entrevistados, e seus exames complementares foram revisados no momento da consulta para o início de tratamento para tuberculose em uma unidade básica de saúde no município de Nova Iguaçu (RJ). **Resultados:** As medianas (e seus respectivos intervalos interquartílicos) para o tempo entre o início dos sintomas e o início do tratamento, o tempo até a procura por atendimento médico, o tempo até o diagnóstico e o tempo até o início do tratamento, em semanas, foram, respectivamente, 11 (6-24), 8 (4-20), 2 (1-8) e 1 (1-1).As variáveis gênero, idade, escolaridade, uso prévio de antibióticos, status HIV, local da primeira consulta médica e extensão radiológica da doença não se associaram ao tempo até o diagnóstico ou ao tempo até o início do tratamento. A principal razão para a demora dos pacientes em procurar o serviço de saúde foi sua dificuldade em reconhecer seus sintomas como indicativos de doença. **Conclusões:** Os tempos até o diagnóstico e até o início do tratamento para tuberculose foram inaceitavelmente longos na amostra estudada.

Descritores: Tuberculose/diagnóstico; Tuberculose/terapia; Diagnóstico tardio.

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Introduction

Although there has been a progressive reduction in tuberculosis incidence rates in the last 10 years, Brazil continues to be one of the 22 countries that collectively account for 80% of all cases of tuberculosis worldwide.[1] In 2009, the World Health Organization (WHO) estimated that the incidence of tuberculosis in Brazil was 45 cases per 100,000 population, and, according to data from the Brazilian National Ministry of Health, the incidence of tuberculosis was 37 cases per 100,000 population in that year.[1,2] Rio de Janeiro is the state with the highest tuberculosis incidence rate (71/100,000 population) in Brazil. Nova Iguaçu is the city with the third highest incidence (76/100,000 population) in the state, after the cities of Rio de Janeiro and Caxias. Nova Iguaçu has an estimated population of 831,000 people, a gross domestic product of three billion Brazilian reals, and a Human Development Index of 0.762, ranking 17th among the Brazilian cities with a total population of 500,000 to 1 million inhabitants. Because tuberculosis is a disease transmitted by the airborne route, breaking the transmission chain, by means of early diagnosis and immediate initiation of treatment, is a key aspect in the strategy to control the transmission of *Mycobacterium tuberculosis* and the onset of new cases of the disease.[1,3]

The main strategy for the diagnosis of new cases of pulmonary tuberculosis, as recommended in the Brazilian National Tuberculosis Control Program guidelines, is to perform sputum smear microscopy for the detection of AFB in patients "with respiratory symptoms", who are defined as individuals who have had cough for three weeks or more.[2] Studies conducted in different epidemiological settings reported that certain factors, such as lack of information on the part of patients, lack of knowledge of tuberculosis on the part of health care workers, lack of investment in effective public health policy, and limited patient access to health care and tests, can be associated with delayed diagnosis of tuberculosis.[4-7]

The objective of the present study was to estimate the time elapsed between the onset of symptoms and the initiation of treatment of pulmonary tuberculosis among treatment-naïve patients with positive sputum smears, and to evaluate the variables associated with delays in diagnosis and in treatment initiation in a city with a high incidence of tuberculosis in the state of Rio de Janeiro.

Methods

This was a descriptive exploratory study conducted between June 1, 2006 and July 31, 2008 at a (public) referral primary health care clinic for tuberculosis in the city of Nova Iguaçu, Brazil. All treatment-naïve tuberculosis patients ≥ 12 years of age with positive sputum smears seeking treatment for pulmonary tuberculosis at the primary health care clinic were invited to participate in the study. All individuals (or their legal guardians, in the case of individuals under 18 years of age) who gave written informed consent underwent a standardized interview with a pretested data collection instrument that was developed specifically for the present study. The instrument included questions regarding personal data (age, level of education, etc.) and variables related to the diagnosis of tuberculosis, such as time since symptom onset, previous use of antibiotics, HIV status, site and date of first medical visit, and radiological extent of tuberculosis. The participants were also asked why they had or had not sought medical attention. In addition, the study team reviewed the sputum smear microscopy results and chest X-rays of the participants. The chest X-rays were independently analyzed by two pulmonologists who were blinded to patient data. In case of disagreement in the final report, a third pulmonologist evaluated the X-ray and issued the report. On the basis of the radiographic images, radiologically extensive tuberculosis was defined as a case in which the affected area was equal to or greater than an entire lobe or in which there was one or more cavities with a total area of least 2 cm. A rapid test for the detection of HIV (Determine® HIV1/2 test; Abbott Brasil, Rio de Janeiro, Brazil) was made available to all participants, except to those with a previously documented positive HIV test result. The exclusion criteria were as follows: having previously received tuberculosis treatment for at least 7 days; not having completed the interview; and having no sputum smear microscopy results. The study was submitted to the board of directors of the primary health care clinic and the coordinators of the Tuberculosis Control Program in the city of Nova Iguaçu, having been approved by the Research Ethics Committee of the Federal University of Rio de Janeiro Clementino

Fraga Filho University Hospital on May 8, 2006 (Process no. 447/06).

The statistical analysis was performed with the Statistical Package for the Social Sciences, version 11.0 (SPSS Inc., Chicago, IL, USA). Time-related variables were measured in weeks and were as follows:

- The variable time from symptom onset to seeking medical attention was defined as the time elapsed between the patient-reported date of symptom onset and the date of the first medical visit.
- The variable time from entry into care to diagnosis was defined as the time elapsed between the date of the first medical visit and the date of the positive sputum smear.
- The variable time from entry into care to treatment initiation was defined as the time elapsed between the date of the positive sputum smear and the date of the visit for treatment initiation.

Other variables analyzed were gender, age, level of education, previous use of antibiotics, HIV status, site of first medical visit (primary health care clinic or emergency room), and radiological extent of tuberculosis. The medians and 25-75% interquartile ranges (IQRs) of the variables were calculated, and the Kruskal-Wallis and Mann-Whitney tests were used in order to compare the groups in terms of the medians. Multiple linear regression analysis, which was adjusted for potential confounding variables, was used for identifying associations between independent and dependent variables. Results were considered significant when $p < 0.05$.

Results

The study included 200 patients with AFB-positive sputum smears, and only 1 patient was excluded (for not having completed the interview). All of the 199 participants initially sought medical attention on their own initiative, on the basis of self-perception of health, meaning that they were ill or though they might be ill. The demographic characteristics of the study sample and the different time intervals from symptom onset (as reported by the patients) to treatment initiation are shown in Table 1. The median age of the patients studied was 35 years (IQR, 25-48 years). In the study sample, 87 patients (44%) had been prescribed nonspecific antibiotics before the diagnosis of tuberculosis. Of those, 42 (48%), 17 (20%), and 10 (11%) reported having used amoxicillin, a respiratory quinolone, and sulfa, respectively, whereas 18 (21%) were unable to provide the name of the antibiotic. In the linear regression analysis, the variables gender, age, level of education, previous use of antibiotics, HIV status, site of first medical visit, and radiological extent of tuberculosis showed no associations with longer time from entry into care to diagnosis or to treatment initiation.

The main reasons for the delay in seeking medical attention, as reported by the patients, were as follows: failure to recognize their symptoms as indicators of a disease, in 77 (38.7%); the cost of transportation to a health care clinic, in 32 (16.1%); difficult access to health care, in 29 (14.6%); lack of time to seek medical attention at a health care clinic, in 25 (12.6%); and belief that their condition would improve spontaneously, in 23 (11.6%). In addition, 13 patients (6.5%) reported no reason.

With regard to the number of medical visits before the diagnosis of tuberculosis, 61 (31%), 59 (30%), and 79 (39%) of the patients reported one, two, and three visits, respectively, with a median of two visits (IQR, 1-3), and 137 (69%) of the patients first sought medical attention at an emergency room. Among those 137 patients, the reported symptoms were cough, bloody sputum, fever, night sweats, and weight loss in 135 (98.5%), 52 (38.5%), 112 (82.0%), 114 (83.0%), and 130 (95.0%), respectively.

Discussion

In the study sample, the time from symptom onset, as reported by the patients, to the initiation of treatment of smear-positive tuberculosis was long (11 weeks), most of this period (8 weeks) being a consequence of patient delay in seeking medical attention, although the time from entry into care (first visit to a health care clinic) to the initiation of treatment of tuberculosis (3 weeks) was also excessive.

A systematic review showed that the total time to diagnosis of smear-positive or culture-positive pulmonary tuberculosis was similar to that found in our sample.[8] Although some studies have demonstrated that a twofold increase in the gross domestic product per capita is associated with a significant reduction in tuberculosis incidence, no association was found between time to diagnosis and socioeconomic status in the

Table 1 - Characteristics of the patients, time from symptom onset to seeking medical attention, and time in the health care system (time from entry into care to diagnosis of tuberculosis and time from entry into care to treatment initiation) in the study sample.[a]

Characteristic	Patients, n	Time prior to entering the health care system	p	Time in the health care system	p		p
		Time from symptom onset to seeking medical attention, weeks		Time from entry into care to diagnosis, weeks		Time from entry into care to treatment initiation, weeks	
Sample as a whole	199	8 (4-20)		2 (1-8)		1 (1-1)	
Female gender	64	12 (5.5-21)	0.06	3.0 (1.0-8.0)	0.44	1 (1-1)	0.41
Male gender	135	8 (4-16)		2.0 (1.0-7.5)		1 (1-1)	
Level of education, years	194		0.34		0.16		0.20
< 5	90	12 (6-16)		3.5 (1-8)		1 (1-1)	
≥ 5	104	8 (4-20)		2.0 (1-7)		1 (1-1)	
HIV status	194		0.08		0.21		0.18
Positive	12	14 (9-30)		4.5 (2.0-27.0)		1 (1-1)	
Negative	182	8 (4-16)		2.0 (1.0-7.5)		1 (1-1)	
Previous use of antibiotics	199		0.52		0.35		0.71
No	112	8 (4-20)		2.0 (1.0-8.0)		1 (1-1)	
Yes	87	8 (4-16)		3.0 (1.5-7.0)		1 (1-1)	
Radiological presentation	182		0.38		0.58		0.67
Limited disease	54	8 (4-17)		2 (1-8)		1 (1-1)	
Extensive disease	128	8 (4-16)		3 (1-8)		1 (1-1)	

[a]Values expressed as median (interquartile range).

countries in which those studies were conducted.[8,9] One possible explanation is the fact that tuberculosis tends to be more prevalent in the segments of society with worse social indicators, regardless of the average economic situation of the country. Brazil, for instance, has a per capita income of more than 8,000 dollars/year and a mean incidence of tuberculosis of 45/100,000 population. However, some cities, such as Rio de Janeiro and Nova Iguaçu, have far higher incidence rates (73/100,000 population and 112/100,000 population, respectively), and, despite the high mean income in Brazil, approximately 49 million Brazilians have a monthly per capita income of up to half the national minimum wage, approximately 54 million having no income. Given that there are notable socioeconomic disparities among regions, states, and cities, as well as among neighborhoods in the same city, the analysis of tuberculosis incidence in parallel with the analysis of the development indices of the respective areas could provide relevant and useful information for the control of tuberculosis.[10-12]

In our study sample, the delay in seeking medical attention was the main factor associated with delayed diagnosis and, consequently, with delayed initiation of pulmonary tuberculosis treatment. This finding is similar to those reported in studies that have been conducted in Ethiopia, Nigeria, and Bangladesh and in which the time from symptom onset to diagnosis of tuberculosis ranged from 7.1 weeks to 11 weeks.[13-15] The main reason for the delay in seeking medical attention, as reported by the patients, was their difficulty in recognizing their symptoms as indicators of "a disease" (not tuberculosis, specifically). These findings differ from those reported in similar studies that have been conducted in different

regions of the world and in which the lack of specific knowledge regarding tuberculosis was reported as being the main reason for the delay in seeking medical attention.[9,13,14,16] In fact, in our study sample, 39% of the patients reported not knowing that their symptoms represented a disease, and 11.5% reported not feeling ill enough to seek medical attention.

The surveillance strategies used in the identification of tuberculosis cases are active surveillance, defined as that in which the health care system actively searches for and identifies tuberculosis cases before patients seek medical attention on their own initiative, and passive surveillance, which corresponds to that in which patients spontaneously seek medical attention (at a primary, secondary, or tertiary health care clinic) because they feel ill.[2,3,17] The present study sample was obtained by passive surveillance, given that all patients spontaneously sought medical attention because they felt ill. For years, passive surveillance was advocated by the WHO as part of the directly observed treatment, short-course strategy.[18] However, because passive surveillance is dependent on the ability of individuals to assess their own well-being and health, as well as on early recognition of signs and symptoms as indicators of a disease, it might have limited results. The results of the present study seem to corroborate that. The fact that the 199 patients included in the present study had advanced disease, as demonstrated by the finding of AFB-positive sputum smears in 100% of the patients and by the presence of radiologically extensive tuberculosis in 70%, strongly suggests that those patients had been ill and had had respiratory symptoms for far longer than the 8 weeks reported. A study conducted at a health care clinic in Rio de Janeiro, Brazil, showed that 50% of the patients diagnosed with pulmonary tuberculosis reported having had cough for less than 2 weeks, although 80% had positive sputum smears, i.e., advanced and communicable disease.[19] This finding suggests that patient-reported duration of cough is not an appropriate indicator to define patients seeking medical attention at health care clinics as being suspected of having tuberculosis, despite the recommendations by the WHO and the Brazilian National Tuberculosis Control Program.[19]

Another cause of delay in seeking medical attention, reported by 12.6% of the patients studied, was limited access to health care clinics, a finding that is similar to those reported in studies conducted in other countries.[13,14,18] The fact that 70% of the patients in the present study initially sought medical attention at an emergency room rather than at a primary health care clinic seems to support the hypothesis that factors associated with access to and receptiveness at primary health care clinics have an influence on the prolonged time to diagnosis of tuberculosis. Although we did not investigate why those patients chose to seek medical attention at emergency rooms rather than at primary health care clinics, we can infer that this is associated with the streamlined care provided in emergency rooms, as well as with the possibility of undergoing ancillary tests, such as imaging tests, at such facilities. An additional problem in the surveillance of patients with suspected tuberculosis by emergency rooms is the lack of biosafety measures for the prevention of tuberculosis, as well as the impossibility of performing smear microscopy for the detection of AFB. It has been reported that public health care facilities are rarely considered appropriate in areas and regions where the prevalence and incidence of tuberculosis are higher, which further impairs the effectiveness of passive surveillance.[15,20]

Because of various factors, among which are the disappointing results of passive surveillance, in 2006, the WHO Second Global Plan to Stop TB incorporated active surveillance and intensified surveillance, both of which require a special effort by the health care system, with the objective of increasing the detection of tuberculosis cases in population groups considered to be at a higher risk for tuberculosis (e.g., tuberculosis contacts and individuals who live in areas of very high incidence).[21] In this context, the objectives of active surveillance and intensified surveillance are to diagnose and treat pulmonary tuberculosis before patients seek medical attention on their own initiative, thereby breaking the chain of transmission, reducing the number of infected contacts, and, consequently, reducing the number of cases of active tuberculosis in the future.

The mean time from the first medical visit to diagnosis of tuberculosis, as reported by the patients, was 2 weeks, and up to 25% of the cases were diagnosed and started on treatment within a total of 8 weeks (IQR, 1-8 weeks). Certain factors, such as an overloaded health care system and the lack of knowledge of tuberculosis on the

part of health care workers, have been reported to be associated with delayed diagnosis of pulmonary tuberculosis, even by a number of health care system administrators.[15,22,23] In our study sample, the patients had, on average, two medical appointments before diagnosis, and, for 58 patients (29%), the diagnosis was made in the first visit, which demonstrates the high degree of suspicion of tuberculosis on the part of physicians. However, the study included only patients with AFB-positive sputum smears, and it takes only a few hours to perform sputum smear microscopy. Therefore, we can consider that the time from entry into care to diagnosis (i.e., 2 weeks) was unacceptably long. The time from the request of sputum smear microscopy in a patient with suspected tuberculosis who is able to expectorate spontaneously (as was the case for the patients in our study sample) to the release of the result (which will subsequently become known to the health care team) is approximately 24 h. In addition, because of the lack of an appropriate place for sputum collection in most primary health care clinics, patients are often instructed to collect sputum at home and return on the following day, which further increases the time to diagnosis and the cost of the procedure for patients. These findings suggest that delayed diagnosis of tuberculosis after entry into care is more closely related to infrastructure problems in the health care system than to the time it takes to perform the diagnostic test or the lack of knowledge on the part of health care workers.

Similarly, the time from obtaining smear microscopy results to the initiation of treatment of tuberculosis (1 week) is inappropriate. The time from obtaining positive smear microscopy results and treatment initiation should not exceed 24-48 h.

The present study has several important limitations. Because our study was conducted at only one primary health care clinic, our findings and conclusions might not be applicable to other primary health care clinics or regions. However, in a recent study, in which the time from symptom onset to diagnosis of tuberculosis was assessed at 20 primary health care clinics and 3 hospitals in the state of Rio de Janeiro, the data obtained were similar to ours, despite the fact that the sample in that study was more heterogeneous.[24] Another limitation is the diagnostic criterion for tuberculosis in the present study (i.e., the presence of AFB in sputum). Although sputum smear microscopy has a high positive predictive value in Brazil, a definitive diagnosis of tuberculosis can only be established by a positive culture for *M. tuberculosis*. In addition, it is possible that including only patients with AFB-positive sputum smears introduced a selection bias for HIV-positive patients, precluding a proper analysis of the impact that HIV infection has on the time from entry into care to diagnosis and to treatment initiation. Furthermore, the fact that the sample consisted mostly of male patients (135/199) might not have allowed a proper assessment of the impact that gender has on the time from entry into care to diagnosis and to treatment initiation. It should also be taken into consideration that the extent of tuberculosis, which was assessed as a predictor, might actually have been a consequence of the time from entry into care to diagnosis. Some of the data in the present study (e.g., duration of symptoms and first medical visit) were obtained through an interview, which might have introduced an information bias in the study.

In conclusion, the time from entry into care to diagnosis and to initiation of treatment of tuberculosis was long in the study sample. The main reason for delayed diagnosis of tuberculosis was patient delay in seeking medical attention, which was due to their inability to recognize that they were ill and to limited access to health care clinics. This delay suggests the need for implementing strategies aimed at early diagnosis of tuberculosis, especially in areas and groups at high risk for tuberculosis. The long time from entry into care to diagnosis of tuberculosis and from obtaining a positive sputum smear to treatment initiation suggests the need for strategies to reduce these time intervals, including investment in infrastructure and in a computerized health care system.

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