Tuberculosis recurrence in a priority city in the state of São Paulo, Brazil

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ABSTRACT

Objective: To describe cases of tuberculosis recurrence (TBR), stratified by temporal classification (early or late TBR), and to identify possible predictors of such recurrence. **Methods:** This was an analytical retrospective observational epidemiological study involving a cohort of 963 new cases of pulmonary tuberculosis, reported and treated via the Tuberculosis Control Program in the city of Carapicuíba, Brazil. The study period was from 2000 to 2010. All of the pulmonary tuberculosis patients who successfully completed the treatment (with or without confirmation of cure) were selected and followed until December 31, 2012. **Results:** Of the 963 cases, TBR occurred in 47 (4.88%). The mean time between the first and second tuberculosis episodes was 36.12 months. Of the 47 TBR cases, 16 (34.04%) occurred within the first 18 months after the completion of the initial treatment (early TBR) and 31 (65.96%) occurred thereafter (late TBR). There were statistically significant differences between the early and late TBR groups only regarding level of education (≤ 3 vs. > 3 years of schooling; p < 0.004) and weight gain at completion of the initial treatment (1.78 kg vs. 5.31 kg; p < 0.045)—not regarding any of the other variables studied. **Conclusions:** A low level of education might translate to poor treatment adherence, which impedes the killing of bacilli and facilitates their survival in a latent state, making it appear as if the treatment was effective. Minimal or no weight gain at completion of the initial treatment might be a reliable biomarker to be used by health care facilities that provide tuberculosis treatment.

Keywords: Recurrence; Tuberculosis; Risk factors.

INTRODUCTION

Tuberculosis, which is considered to be a curable disease, is one of the oldest diseases known to mankind. Short-term treatment regimens combining rifampin, isoniazid, pyrazinamide, and ethambutol have an efficacy of nearly 100% provided that the drugs are administered in the correct doses and for the appropriate amount of time in drug-susceptible patients; however, tuberculosis remains a serious public health problem in the 21st century.[1-4] The World Health Organization estimates that over 9 million people have had tuberculosis; of those, 1.5 million have died, whereas 300,000 have developed the disease again after having been treated and considered cured,[3] constituting cases of tuberculosis recurrence (TBR).

Studies have shown that the risk of TBR is higher in previously treated tuberculosis patients than in the general population, being up to four times higher in the former than in the latter depending on the epidemiological profile of the disease at the study site.[5,6] A major concern for tuberculosis control programs (TCPs), TBR is overlooked and understudied by researchers and health authorities alike. TBR rates vary widely, being 0.4% in patients receiving directly observed treatment, short-course (DOTS) and over 30% in appropriately treated patients receiving self-administered treatment.[7-9]

TBR is due to endogenous reactivation (also known as relapse), caused by the same bacterial strain that caused the first episode of tuberculosis (probably because of bacillary persistence), or exogenous infection (also known as reinfection) with a new strain of *Mycobacterium tuberculosis*. Although there is no clinical difference between relapse and reinfection, they can be differentiated by using molecular biology techniques, which are usually unavailable in routine clinical practice.[5,8,10-12] According to the British Medical Research Council, 91% of relapses occur before post-discharge month 12, and a recent review of the latest clinical trials of new tuberculosis treatment regimens showed that 94% of relapses occurred within the first 18 months after treatment completion.[13] TBR can be classified as early TBR or late TBR; the former is defined as TBR occurring within the first 18 months after treatment completion, whereas the latter is defined as TBR occurring thereafter.[6,8,12,14]

A better knowledge and understanding of TBR will improve the surveillance and follow-up of tuberculosis patients discharged from treatment, thus improving disease control and contributing to breaking the chain of transmission. The objective of the present study was to describe cases of early and late TBR in a cohort of patients treated via a municipal TCP and to identify possible predictors of such recurrence.

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METHODS

Characterization of the study site

The present study was conducted in the city of Carapicuíba, Brazil, a bedroom community in the greater metropolitan area of São Paulo. The latest census showed that Carapicuíba had a population of 369,908 inhabitants, being one of the most densely populated cities in the country (i.e., 10,576 people/km^2). In 1995, the *Programa Nacional de Controle da Tuberculose* (PNCT, Brazilian National Tuberculosis Control Program) identified the city of Carapicuíba as a priority because of its high burden of tuberculosis, with a mean incidence of 41.77 cases per 100,000 population in the last 5 years.[15] The local TCP was launched in the 1990s and, on the basis of epidemiological criteria, has been considered a priority by the Brazilian National Ministry of Health since then. In 2004, the DOTS strategy was implemented in all primary care clinics in the city via the local TCP, the decentralization of diagnosis being achieved by actively searching for patients with respiratory symptoms and collecting samples for smear microscopy at all public health care facilities. A rapid molecular biology-based assay has recently been implemented.

Study design

This was an analytical retrospective observational epidemiological study involving a cohort of new cases of tuberculosis, reported and treated via the TCP in the city of Carapicuíba. The study period was from 2000 to 2010. All of the pulmonary tuberculosis (PTB) patients who successfully completed the treatment (with or without confirmation of cure, as defined by the PNCT) were selected and followed until December 31, 2012 (Figure 1). The inclusion, exclusion, and follow-up criteria were those used in a larger study approved by the Research Ethics Committee of the Federal University of São Paulo (Protocol no. 0690/11).[15] TBR (the dependent variable) was defined as a second episode of tuberculosis after completion of the initial treatment, being classified as early or late TBR. Early TBR was defined as PTB occurring within the first 18 months after treatment completion. Late TBR was defined as PTB occurring more than 18 months after treatment completion.
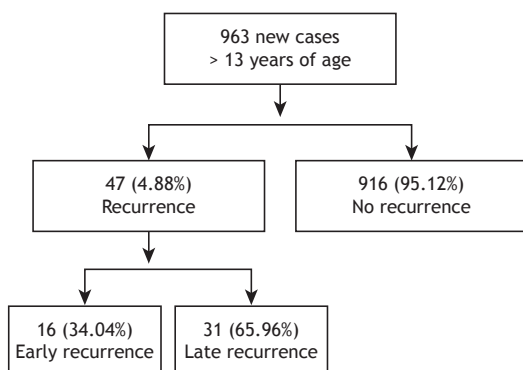
Data source and variables analyzed

Data were collected from the São Paulo State Epidemiological Surveillance Tuberculosis System (Epi-TB database) and the Online Epidemiological Surveillance Tuberculosis System (TBweb database) for the 2000-2005 and 2006-2010 periods, respectively. All data collected from the TBweb database were collected in real time. After identification of the medical record numbers, patient medical records were retrieved for data collection. Data were collected with the use of questionnaires developed specifically for the present study, being subsequently entered into an Epi Info 3.3 database. Double data entry and the Epi Info "data compare" tool were used in order to verify data consistency and eliminate typographical errors.

For the first episode of PTB, the following independent variables were analyzed: sociodemographic variables (gender, age, level of education, occupation—in accordance with the Brazilian Institute of Geography and Statistics—and household contact); comorbidities/unhealthy habits (diabetes mellitus, HIV infection, alcoholism, smoking, and drug addiction); signs and symptoms (time from onset of signs and symptoms to treatment, cough, fever, and sweating); clinical variables (active PTB, bilateral pulmonary involvement, and pulmonary cavitation); health and diagnostic equipment (place of treatment and type of facility); and treatment-related variables (number of doses taken during self-administered treatment, number of doses taken during DOTS, number of doses missed during DOTS, weight gain—in kg—in the attack phase, weight gain—in kg—at discharge from treatment, negative smear results in the attack phase, adverse events during treatment, and home contact with active tuberculosis during follow-up).

Statistical analysis

A frequency distribution table showing absolute and relative values was constructed to describe the characteristics of TBR cases. In order to determine the association between independent variables and the dependent variable (early or late TBR), the chi-square test was used, Yates' correction or Fisher's exact test being used when necessary; for risk assessment, prevalence ratios (PRs) were used, with a 95% CI and a significance level of $p \leq 0.05$; for continuous variables related to early or late TBR (independent groups), the Student's t-test (Levene's test) or the Mann-Whitney (Kruskal-Wallis) test was used, with a significance level of $p \leq 0.05$. All statistical analyses were performed with the IBM SPSS Statistics software package, version 20 (IBM Corporation, Armonk, NY, USA).

RESULTS

By the end of the follow-up period, TBR had occurred in 47 (4.88%) of the 963 PTB patients in our cohort;

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┌─────────────────────┐
│   963 new cases     │
│  > 13 years of age  │
└─────────────────────┘
           │
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┌──────────┐ ┌──────────────┐
│47 (4.88%)│ │916 (95.12%)  │
│Recurrence│ │No recurrence │
└──────────┘ └──────────────┘
     │
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│16 (34.04%) │ │31 (65.96%) │
│Early       │ │Late        │
│recurrence  │ │recurrence  │
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Figure 1. Flowchart of pulmonary tuberculosis cases in the city of Carapicuíba, Brazil, in the 2000-2012 period.

in half of the cases, TBR occurred within 34 months after treatment completion. The mean time between treatment and TBR was 36.12 months (range, 2.52-98.04 months). Of the 47 cases of TBR, 7 (14.89%) occurred within the first 6 months after treatment completion, whereas 13 (27.66%) and 16 (34.04%) occurred within the first 12 and 18 months, respectively, and were therefore considered to be cases of recent TBR; the remaining 31 TBR cases (65.96%) occurred more than 18 months after treatment completion and were therefore considered to be cases of late TBR (Figure 2).

Of the 47 patients in whom there was TBR, 35 (74.47%) were male, and the mean age was 32.77 years. Approximately 45% had had ≥ 8 years of schooling. Most of the patients were currently employed (70.22%) and had home contacts (93.62%). The most prevalent comorbidity was diabetes mellitus (in 14.89%), and the most prevalent unhealthy habit was smoking (in 44.68%). Cough was reported by most of the patients (97.87%). With regard to the clinical variables, 80.85% of the patients had active tuberculosis (positive smear results at diagnosis), 63.83% had bilateral pulmonary involvement, and 57.45% had imaging findings suggestive of pulmonary parenchymal cavitation; only 8.51% had been diagnosed at private facilities, and slightly more than half had been diagnosed in an emergency room or hospital.

The mean number of doses taken during self-administered treatment was 92.27, and the mean number of doses taken during DOTS was 84.73; although 46.81% of the patients experienced adverse events during the initial treatment, only 1 (4.54%) experienced a major adverse event (drug hepatotoxicity), with no need to change the standard regimen. There was weight gain at the end of the attack phase in 74.47% and at discharge from treatment in 82.98%. In addition, approximately 15% had household contacts with active tuberculosis during treatment.

A bivariate analysis of the association between categorical variables and early or late TBR (Table 1) showed that the level of education was the only significant variable ($p \leq 0.05$); that is, a lower level of education translated to a greater association with early TBR (PR = 1.70 for up to 3 years of schooling; PR = 1.59 for 4-7 years of schooling). None of the other categorical variables were found to have statistical significance. A bivariate analysis of the association between quantitative variables and early or late TBR (Table 2) showed that weight gain (in kg) at discharge from treatment was the only significant variable, the mean weight gain being 1.78 kg for the early TBR group and 5.31 kg for the late TBR group.

DISCUSSION

The proportions of TBR cases vary widely across studies, ranging from 0.4% to 61.7%[4,6,9,16-20]; the incidence of TBR in the present study is consistent with that reported in locations where there are well-structured TCPs (i.e., 5-6%).[21,22] The incidence of TBR in the present study is also consistent with that reported in locations where the reported incidence of tuberculosis is low, such as North America and Australia,[16,18] moderate, such as Brazil and Spain,[19,20] and high, such as South Africa and Ethiopia,[4,20] regardless of heterogeneity and tuberculosis burden.[3,4,6,12,16-20]

Cases of relapse occur toward the end of the treatment period, primarily between months 6 and
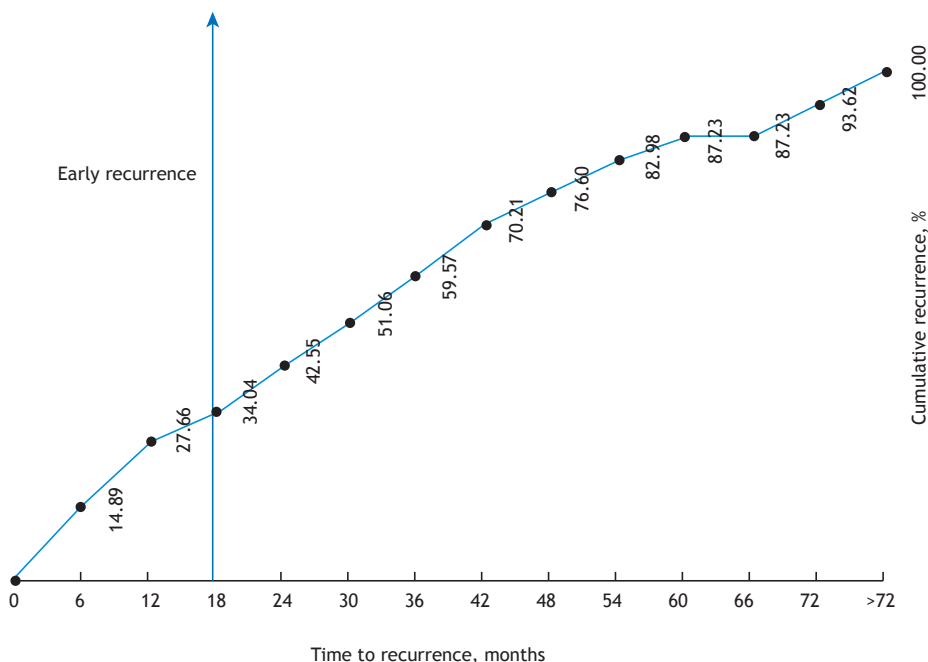
Figure 2. Cumulative recurrence of pulmonary tuberculosis during follow-up (in months) in the city of Carapicuíba, Brazil, in the 2000-2012 period.

Table 1. Frequency distribution and prevalence ratio, by type of pulmonary tuberculosis recurrence, in the city of Carapicuíba, Brazil, in the 2000-2012 period.

Variable	Total	%	Recurrence				PR	95% CI	p
			Early		Late				
			n	%	n	%			
TOTAL	47	100.00	16	34.04	31	65.96			
Gender									
Male	35	74.47	11	31.43	24	68.57		0.58-3.04	0.518
Female	12	25.53	5	41.67	7	58.33	1.33		
Level of education, number of years of schooling									
≤ 3	8	17.02	6	75.00	2	25.00	1.70	1.19-2.42	0.004
4-7	18	38.30	4	22.22	14	77.78	1.59	1.11-2.27	0.011
≥ 8	21	44.68	6	28.57	15	71.43			
Occupation									
Unemployed	7	14.89	4	57.14	3	42.86	1.39	0.94-2.06	0.102
Employed	33	70.22	8	24.24	25	75.76	1.00	0.60-1.68	1.000
Other	7	14.89	3	42.86	4	57.14			
Household contact									
No	3	6.38	0	0.00	3	100.00			
Yes	44	93.62	16	36.36	28	63.64			
Diabetes									
No	40	85.11	13	32.50	27	67.50			
Yes	7	14.89	3	42.86	4	57.14	1.32	0.50-3.46	0.676
HIV infection									
No	45	95.74	15	33.33	30	66.67			
Yes	2	4.26	1	50.00	1	50.00	1.50	0.35-6.37	0.626
Alcoholism									
No	33	70.21	12	36.36	21	63.64	1.27	0.50-3.27	0.742
Yes	14	29.79	4	28.57	10	71.43			
Smoking									
No	26	55.32	10	38.46	16	61.54	1.35	0.59-3.10	0.477
Yes	21	44.68	6	28.57	15	71.43			
Drug addiction									
No	41	87.23	15	36.58	26	63.42	2.20	0.35-13.74	0.648
Yes	6	12.77	1	16.67	5	83.33			
Time from onset of signs/symptoms to treatment, weeks									
≤ 3	4	8.51	1	25.00	3	75.00			
≥ 4	43	91.49	15	34.88	28	65.12	1.40	0.24-8.00	0.690
Cough									
No	1	2.13	1	100.00	0	0.00			
Yes	46	97.87	15	32.61	31	67.39			
Fever									
No	8	17.02	3	37.50	5	62.50	1.13	0.41-3.05	0.821
Yes	39	82.98	13	33.33	26	66.67			
Sweating									
No	7	14.89	3	42.86	4	57.14	1.32	0.50-3.46	0.676
Yes	40	85.11	13	32.50	27	67.50			
Active tuberculosis									
No	9	19.15	5	55.56	4	44.44	1.92	0.89-441	0.239
Yes	38	80.85	11	28.95	27	71.05			
Bilateral involvement									
No	17	36.17	5	21.41	12	78.59			
Yes	30	63.83	11	36.67	19	63.33	1.25	0.52-2.99	0.614
Pulmonary cavitation									
No	20	42.55	6	30.00	14	60.00			
Yes	27	57.45	10	37.04	17	62.96	1.23	0.54-2.83	0.615
Place of treatment									
Outpatient clinic	23	48.93	9	39.13	14	60.87	1.34	0.60-3.00	0.471
Other[a]	24	51.07	7	29.17	17	70.83			
Type of facility									
Public	43	91.49	14	32.56	29	67.44			
Private	4	8.51	2	50.00	2	50.00	1.54	0.53-4.48	0.598
Negative smear results in the attack phase									
Yes	33	70.21	10	30.30	23	69.70			
No	14	29.79	6	42.86	8	57.14	1.41	0.64-3.13	0.406
DOTS									
No	28	59.57	10	35.71	18	64.29	1.13	0.49-2.59	0.769
Yes	19	40.43	6	31.58	13	68.42			
Adverse events									
No	25	53.19	8	32.00	17	68.00			
Yes	22	46.81	8	36.36	14	63.64	1.14	0.51-2.52	0.753
Home contacts with active tuberculosis									
No	40	85.11	13	32.50	27	67.50			
Yes	7	14.89	3	42.86	4	57.14	1.32	0.50-3.46	0.676

PR: prevalence ratio; and DOTS: directly observed treatment, short-course. [a]Emergency room or hospital.

Table 2. Variables, by recurrence type, in the city of Carapicuíba, Brazil, in the 2000-2012 period.

Variable	Recurrence		Difference[a]	p
	Early Mean	Late Mean		
Age, years	37.94	30.10	7.84	0.096
Doses taken during SAT, n	99.57	88.50	11.07	0.667
Doses taken during DOTS, n	85.00	84.89	0.11	0.419
Doses missed during DOTS, n	11.22	2.19	9.03	0.119
Weight gain within 60 days after treatment initiation, kg	1.11	3.39	2.27	0.108
Weight gain at treatment completion, kg	1.78	5.31	3.53	0.045

SAT: self-administered treatment; and DOTS: directly observed treatment, short-course. [a]Expressed as absolute values.

12[13,14]; therefore, in phase III clinical trials examining the efficacy of new drugs or treatment regimens for tuberculosis, patients are followed until 18 months after discharge from treatment (cure).[13] Relapse, which is also known as endogenous reactivation, is caused by the same bacterial strain that caused the first episode of tuberculosis (probably because of bacillary persistence). The term persistence refers to the ability of bacilli to survive dormant within alveolar macrophages or in caseous areas even when they are sensitive to antituberculosis drugs and when bactericidal concentrations of chemotherapeutic agents are adequate during treatment. When conditions are favorable, these bacilli become metabolically active and multiply. When they multiply during treatment, they are completely eliminated by chemotherapy; however, if they resume their metabolic activity after discharge from treatment, TBR occurs.[13,23-26]

Several studies[8,12,19,26-30] have shown that TBR resulting from exogenous reinfection occurs long after treatment completion, more consistently over time and predominantly in locations where the burden of tuberculosis is moderate or high, because the chain of transmission is active. This was confirmed experimentally in a laboratory setting,[21] cured animals having subsequently developed a transient specific antigenic immune response that decreased over time. This transient resistance appears to prevent hematogenous spread of new bacilli and, consequently, a second episode of tuberculosis caused by early exogenous infection.

In the present study, a low level of education was found to be a risk factor for early TBR, possibly interfering with treatment adherence. The number of doses taken during self-administered treatment was higher in the early TBR group than in the late TBR group, although the difference was not statistically significant; however, it was impossible to determine the exact number of doses taken during treatment. It can be hypothesized that treatment adherence was lower in the early TBR group, a hypothesis that supports the recommendation of the World Health Organization and several groups of authors that DOTS be used.[3,14,16,19,24] Tuberculosis is a disease that has long been associated with poverty and low socioeconomic development, as indirectly measured by little or no schooling[9,10,12,31]; therefore, poverty can be associated with poor health status, or

the latter can affect work and working conditions or limit job opportunities. This can also have an impact on treatment adherence,[14,16,19,24] thus explaining the aforementioned biological mechanism for bacillary persistence in cases of TBR, a mechanism that has been confirmed in other studies.[32,33]

In the present study, early TBR was found to be associated with reduced weight gain at discharge from treatment, a finding that suggests greater activation of tuberculosis-related chemical mediators, slower normalization of those mediators, or a combination of the two. In a clinical trial,[34] it was found that, among individuals who were underweight at diagnosis, weight gain of 5% or less during treatment was associated with an increased risk of TBR. An association between weight loss and TBR has been found in observational studies[35-37] and in laboratory animal studies,[23,33] as well as having been found in an operational study conducted in Bangladesh.[38] Weight loss and malnutrition are common in patients with tuberculosis; however, it is difficult to distinguish between cause and effect. The fact that TNF-α is released into the bloodstream of tuberculosis patients by sensitized phagocytic cells and that TNF-α is related to weight loss and cachexia can partially explain why weight loss is a common complaint in patients with tuberculosis.[32-36] In addition to TNF-α, the concentrations of IL-1, IL-6, IFN-γ, and prostaglandins are altered in individuals with cachexia, emphasizing the role of chronic diseases, such as tuberculosis, in the process of weight loss.[37]

Potential limitations of the present study include recall and information biases. It is possible that the answers that the patients themselves or their legal guardians gave to questions regarding some of the exposure variables, such as time from onset of signs and symptoms to treatment, cough, fever, and sweating, resulted in recall bias. It is also possible that their answers to questions regarding comorbidities and unhealthy habits, such as alcoholism, smoking, and drug addiction, resulted in information bias. Therefore, there is a possibility that these two potential biases affected the significance of the aforementioned variables. Another limitation is that it was impossible to control for confounding variables because of the small number of TBR cases during the follow-up period, a stratified or multivariate statistical analysis of early and late TBR therefore being impossible. Yet another limitation

is that it was impossible to distinguish between TBR resulting from endogenous reactivation and TBR resulting from exogenous reinfection. Molecular biology methods are not routinely used in Brazil as they are in countries such as the United States. However, this does not invalidate the results of the present study. One strength of the present study is that it was a retrospective observational study of secondary data from a municipal TCP, such data being much more representative of daily clinical and operational practices than are those from controlled clinical trials.

In summary, the present study showed that TBR cases occurring within the first 18 months after treatment completion (early TBR cases) were more common than late TBR cases, the occurrence of which increased consistently thereafter, a finding that is consistent with the literature. A low level of education might translate to poor treatment adherence, which impedes the elimination of bacilli and facilitates their survival in a latent state, making it appear as if the treatment was effective, as observed in the present study. One strategy to reduce early TBR, as well as for cases in which there is minimal or no weight gain at treatment completion, is to prolong treatment on the basis of the number of doses missed during DOTS, as recommended by the PNCT. Although minimal or no weight gain at treatment completion might be a reliable biomarker to be used by health care facilities that provide tuberculosis treatment, further studies of TBR are needed in order to confirm that.

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