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Factors associated with tuberculosis retreatment in priority districts of Maranhão, Brazil

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Abstract *This study investigated factors associated with cases of tuberculosis retreatment due to relapse and readmission after treatment abandonment. This is an analytical cross-sectional study type of cases reported in the Information System for Notifiable Diseases in priority municipalities in the State of Maranhão, from January 2005 to December 2010. A logistic regression model was used to identify the association. Patients aged between 40 and 59 years (OR = 1.49, p = 0.029) with a pulmonary clinical form (OR = 2.79, p = 0.016) were more likely to incur relapse. Readmissions after abandonment were more likely in males (OR = 1.53, p = 0.046), aged between 20 and 39 years (OR = 1.65, p = 0.007), with less than eight years of schooling (OR = 2.01, p = 0.037) and with alcohol dependence (OR=1.66, p = 0.037), which showed a higher probability of another abandonment (OR = 5.96, p < 0.001). These data reinforce the need for strategies aimed at this group, such as increased supervised treatment, intensified active search, post-discharge follow-up and health education action.*

Key words *Tuberculosis, Retreatment, Relapse*

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Introduction

Tuberculosis is a serious public health problem and the second leading cause of death from infectious diseases worldwide. Currently, a third of the world's population is infected by the *Mycobacterium tuberculosis* bacillus, of which 10% will develop the disease, which corresponds to approximately 9 million new cases per year[1].

One of the current greatest challenges to TB control in Brazil is case retreatment. This group formed by relapse and readmission cases shows a greater probability of developing an unfavorable outcome for the disease, such as death, re-abandonment and resistance to treatment drugs, which is an additional threat to TB control, implying more expensive and more complicated treatment[2,3]. In Brazil, 96% of reported resistance cases are acquired, with more than half having a history of three or more previous treatments[4].

According to Hijar et al.[5], in Brazil, about 15,000 cases of retreatment due to relapse or readmission after abandonment are reported annually, which, together with new cases, is the 9th cause of hospitalizations due to infectious diseases, ranking 7th in hospitalization expenses of the Unified Health System (SUS) for infectious diseases and is the 4th cause of mortality due to infectious diseases.

Relapses are characterized by the persistence of bacilli in allegedly healed patients, and may occur by reinfection (exogenous relapse) or reactivation (endogenous relapse). In general, early relapses are associated with endogenous reactivation, characterized by bacillus survival capacity even in the presence of bactericidal concentrations of chemotherapeutics during correctly conducted treatments[6,7].

Persistent bacilli are not necessarily resistant to drugs, but may have slow or irregular metabolism. By finding favorable conditions that compromise bacillary destruction, such as the low immunological conditions caused by AIDS, diabetes, alcohol abuse, neoplasms, malnutrition and the use of corticosteroids, they become metabolically active and multiply again, facilitating the development of relapses[6,8,9]. Late relapses are more associated with exogenous reinfection, especially in regions where incidence is high and social conditions are poor, which exposes individuals to new infections[2,10,11]. Ruffino-Netto[7] suggests that current diagnostic tests such as polymerase chain reaction (PCR) could elucidate the nature of the process (reinfection or reactivation).

Readmission after abandonment is characterized by the return of patients to the treatment after missing therapy for more than thirty days, from the date scheduled for their return[6]. Treatment abandonment has been pointed out by several studies as a serious problem that leads to the maintenance of the bacillus transmission chain, since the patient not treated properly continues as a source of infection, increasing the risk of disease and mortality aggravation and favoring the development of drug-resistant bacteria, hampering disease control[12].

According to Ruffino-Neto[7], few studies investigate the issue of retreatment, which is an important monitoring indicator of the National Tuberculosis Control Program (PNCT), since it allows the identification of the program's performance in relation to case retrieval. Retreatments may be associated with both programmatic organizational factors and individual factors[6]. Knowledge of factors associated with retreatment is a subsidy to the improvement of control strategies, directing treatment and follow-up, with a view to reducing unfavorable outcomes. Thus, this study aims to investigate factors associated with cases of retreatment due to relapse and readmission after abandonment.

Methodology

This is an analytical cross-sectional study of tuberculosis cases reported in the priority municipalities for TB control in the state of Maranhão, from 2005 to 2010.

The State of Maranhão is located in Northeast Brazil and has an area of 333,935.507 Km^2 and a population of 6,574,789 inhabitants[13]. It has 217 municipalities, eight of which are priority for TB control (Açailândia, Caxias, Codó, Imperatriz, Paço do Lumiar, São José de Ribamar, São Luís and Timon), as they have more than 100,000 inhabitants and a high incidence of TB (mean of 36.4/100,000 inhabitants in 2011).

The population was established by all cases of tuberculosis reported in the Notifiable Diseases Information System (SINAN) in the priority municipalities of the State of Maranhão, from January 1, 2005 to December 31, 2010.

Inclusion criteria were new cases and retreatment cases (relapse and readmission) of pulmonary and extrapulmonary tuberculosis. The type of admission due to transfer and change of diagnosis was the exclusion criterion.

A new patient with tuberculosis who never underwent TB chemotherapy or who used tuber-

culostatics for less than 30 days was considered a new case; cases of relapse (active disease after previous treatment and discharge due to cure) and readmission cases (return to treatment after abandonment for more than sixty days from the last visit) were considered retreatment.

Information was collected from the SINAN database of the State Health Secretariat of Maranhão saved in Tabwin version 3.5 and exported to Excel (Microsoft Corp., USA). Next, all variables that could identify individuals were excluded, protecting identification data confidentiality of each case; inconsistencies (inaccurate information), incompleteness (incomplete information) and duplicates (two or more records for the same case) were also excluded.

Study variables

Retreatment (relapse and readmission) was considered as a dependent variable or response. The independent variables selected were gender (male and female), age (≤ 19, 20 to 39, 40 to 59, ≥ 60 years), ethnicity / skin color (white and non-white), schooling in years of study (< 8 and ≥ 8), residence area (rural and urban), clinical form (pulmonary and extrapulmonary), having AIDS (yes and no), alcohol abuse (yes and no), diabetes (yes and no), mental disease (yes and no) and development (cure, abandonment, death and drug-resistant tuberculosis DRTB).

Data review

Statistical analyses were performed in the STATA program, version 11.0 (Stata Corp., College Station, USA). A simple logistic regression model was used to identify the factors associated with retreatment (relapse and readmission). Variables whose value of $p \leq 0.20$ were included in the multiple logistic regression model to adjust for possible biases. Variables were selected with the stepwise method with retrograde elimination of variables. The variables with value of $p \leq 0.05$ remained in the final model. Odds ratios (OR) and their respective 95% confidence intervals (95% CI) were estimated. Reference categories were assigned OR = 1.

Ethical aspects

The Research Ethics Committee of the University Hospital of the Federal University of Maranhão (HUUFMA) evaluated and approved the study, under opinion 240/11, in compliance with the requirements of Resolutions 196/96 and 466/12 of the National Health Council.

Results

Between January 2005 and December 2010, the total number of TB cases in the State of Maranhão arrived at 2,277. Of these, 1991 (87.4%) were new cases, 138 (6.1%) were relapses and 148 (6.5% %) readmission after abandonment.

In the unadjusted analysis, the age ranges 40-59 years ($p = 0.007$) and ≥ 60 years ($p = 0.058$), having pulmonary tuberculosis ($p = 0.012$) and AIDS ($p = 0.035$) were significantly associated with disease relapse (Table 1).

Variables that showed a significant association with readmission were male ($p < 0.001$), age between 20 and 39 years ($p = 0.07$), having less than eight years schooling ($p = 0.015$), having pulmonary tuberculosis ($p = 0.013$), being dependent on alcohol ($p < 0.001$), not having supervised treatment ($p < 0.001$), and termination due to abandonment ($p < 0.001$ (Table 2).

After adjusting the model, relapse rates were: between 40 and 59 years old (OR = 1.49, 95%CI = 1.04-2.13, $p = 0.029$) and having pulmonary TB (OR = 2.79, 95%CI = 1.21-6.43, $p = 0.016$). Regarding readmission, male gender (OR = 1.53, 95%CI = 1.01-2.33, $p = 0.046$), age between 20 and 39 years (OR = 1.65, 95%CI = 1.47-2.38; $p = 0.007$), having less than eight years schooling (OR = 2.01, 95%CI = 1.04-3.89, $p = 0.037$), being dependent on alcohol (OR = 1.66, CI95% = 1.03-2.67; $p = 0.037$) and termination due to abandonment (OR = 5.96, 95%CI = 4.13-8.60, $p < 0.001$) remained as associated factors (Table 3).

Discussion

The results of this study showed a prevalence of disease relapse of 6.1% and readmission to treatment of 6.5%, which is relatively low when studied separately. On the other hand, retreatment (relapse and readmission) represents a percentage of 12.6%, higher than the 10.0% estimated by the Ministry of Health[7,14], but close to the 13.9% reported by Diniz et al.[15] in eight municipalities of Brazilian capitals and less than the 17.8% of Vieira and Leitão[16] study carried out in Fortaleza.

It should be pointed out that because it is a cross-sectional study, the odds ratio (OR) was chosen because prevalence of disease relapse and retreatment were less than 10%, since OR tends

Table 1. Non-adjusted analysis of the factors associated with cases of retreatment of tuberculosis due to relapse, reported in the priority municipalities of Maranhão, in the period 2005-2010.

Variables	New cases (N = 1991) n (%)	Relapse (N = 138) n (%)	OR (CI 95%)	*p*
Gender				
Female	704 (92.9)	54 (7.1)	1	
Male	1,287 (93.9)	84 (6.1)	0.85 (0.60 - 1.21)	0.371
Age				
<19 years	212 (97.3)	6 (2.7)	1	
20 to 39 years	792 (93.9)	51 (6.1)	2.27 (0.96 - 5.37)	0.061
40 to 59 years	588 (91.6)	54 (8.4)	3.24 (1.37 - 7.65)	0.007
≥ 60 years	399 (93.7)	27 (6.3)	2.39 (0.97 - 5.88)	0.058
Ethnicity				
White	321 (94.7)	18 (5.3)	1	
Non white	1,670 (93.3)	120 (6.7)	1.28 (0.77 – 2.13)	0.340
Schooling				
> 8 years	296 (92.5)	24 (7.5)	1	
≤ 8 years	1,695 (93.7)	114 (6.3)	0.83 (0.52 – 1.31)	0.423
Area				
Rural	428 (94.1)	27 (5.9)	1	
Urban	1,563 (93.4)	111 (6.6)	1.12 (0.73 – 1.73)	0.593
Clinical form				
Extrapulmonary	232 (97.5)	6 (2.5)	1	
Pulmonary	1,759 (93.0)	132 (7.0)	2.9 (1.26 – 6.65)	0.012
Aids				
No	1,834 (93.9)	120 (6.1)	1	
Yes	157 (89.7)	18 (10.3)	1.75 (1.04 – 2.95)	0.035
Alcohol abuse				
No	1,828 (93.7)	123 (6.3)	1	
Yes	163 (91.6)	15 (8.4)	1.37 (0.78 – 2.39)	0.273
Diabetes				
No	1,842 (93.5)	128 (6.5)	1	
Yes	149 (93.7)	10 (6.3)	0.96 (0.49 – 1.88)	0.918
Mental disease				
No	1,921 (93.6)	132 (6.4)	1	
Yes	70 (92.1)	6 (7.9)	1.25 (0.53 – 2.92)	0.611
Development				
Cure	1,451 (93.5)	100 (6.4)	1	
Abandonment	234 (93.6)	16 (6.4)	0.99 (0.57 – 1.71)	0.977
Death	293 (93.3)	21 (6.7)	1.04 (0.63 – 1.67)	0.875
DRTB	13 (92.9)	1 (7.1)	1.11 (0.14 – 8.61)	0.916

The associated factors were identified by the logistic regression model. Odds Ratio (OR). Confidence Interval (CI). Drug-Resistant Tuberculosis (DRTB).

to overestimate associations and produce false positives when event prevalence is high (usually above 10%).

The prevalence of relapses and readmissions to treatment found in this study showed discrepancies vis-à-vis findings in literature. Relapses were higher than the 4.3% found by Picon et al.[17] in Rio Grande do Sul and lower than the 7.8% recorded by Yamagishi and Toyota[18] in Japan. Likewise, readmissions were lower than the 9.9% registered by Barbosa and Costa[19] in the city of Natal, but higher than the 3.6% described by Furlan et al.[20] in the state of Paraná. Some studies have shown frequencies of readmission below those of abandonment[21,22]. This difference can perhaps be explained by the fact that some cases

Table 2. Non-adjusted analysis of the factors associated with cases of retreatment of tuberculosis by readmission, reported in the priority municipalities of Maranhão, in the period 2005-2010.

Variables	New cases (N = 1991) n (%)	Readmission (N = 148) n (%)	OR (CI 95%)	*p*
Gender				
Female	704 (95.5)	33 (4.5)	1	
Male	1287 (91.8)	115 (8.2)	1.90 (1.28-2.40)	<0.001
Age				
<19 years	212 (95.9)	9 (4.1)	1	
20 to 39 years	792 (90.0)	88 (10.0)	2.62 (1.30 – 5.28)	0.007
40 to 59 years	588 (94.7)	33 (5.3)	1.32 (0.62 – 2.80)	0.468
≥ 60 years	399 (95.7)	18 (4.3)	1.06 (0.47 – 2.40)	0.884
Ethnicity				
White	321 (95.3)	16 (4.7)	1	
Non white	1670 (92.7)	132 (7.3)	1.58 (0.93 – 2.70)	0.090
Schooling				
> 8 years	296 (96.4)	11 (3.6)	1	
≤ 8 years	1695 (92.5)	137 (7.5)	2.17 (1.16 – 4.06)	0.015
Area				
Rural	428 (92.8)	33 (7.2)	1	
Urban	1563 (93.2)	115 (6.8)	0.95 (0.64 – 1.42)	0.819
Clinical form				
Extrapulmonary	232 (97.1)	7 (2.9)	1	
Pulmonary	1759 (92.6)	141 (7.4)	2.65 (1.22 – 5.74)	0.013
Aids				
No	1834 (92.9)	140 (7.1)	1	
Yes	157 (95.1)	8 (4.9)	0.67 (0.32 – 1.40)	0.278
Alcohol abuse				
No	1828 (93.9)	118 (6.1)	1	
Yes	163 (84.5)	30 (15.5)	2.85 (1.85 – 4.40)	<0.001
Diabetes				
No	1842 (92.8)	142 (7.2)	1	
Yes	149 (96.1)	6 (3.9)	0.52 (0.23 – 1.20)	0.127
Mental disease				
No	1921 (93.2)	141 (6.8)	1	
Yes	70 (90.9)	7 (9.1)	1.36 (0.61 – 3.02)	0.446
Development				
Cure	1451 (95.9)	62 (4.1)	1	
Abandonment	234 (76.5)	72 (23.5)	7.20 (5.00– 10.39)	<0.001
Death	293 (95.7)	13 (4.3)	1.04 (0.56 – 1.91)	0.904
DRTB	13 (92.9)	1 (7.1)	1.80 (0.23– 14.00)	0.754

The associated factors were identified by the logistic regression model. Odds Ratio (OR). Confidence Interval (CI). Drug-Resistant Tuberculosis (DRTB).

of abandonment, when they return to the service, are notified as a new case and not as readmission.

Relapses were associated in adults older than 40 years, similar to the findings of Oliveira and Moreira Filho[6], but different from the findings of Picon et al.[17], who did not find association with age. This association of relapse with age can be explained as resulting from decreased immunity, concomitant diseases and malnutrition.

The relationship between readmission after abandonment and young adults is a reflection of lower adherence to treatment and higher percentage of abandonment in this age group[23,24]. This behavior is explained by the better percep-

Table 3. Adjusted analysis of the factors associated with cases of retreatment of tuberculosis (relapse and readmission), reported in the priority municipalities of Maranhão, in the period 2005-2010.

Variables	Re-treatment			
	Relapse OR (CI 95%)	*p*	Readmission OR (CI 95%)	*p*
Gender				
Female	1		1	
Male	0.74 (0.52 – 1.08)	1.22	1.53 (1.01 – 2.33)	0.046
Age				
<19 years	1		1	
20 to 39 years	1.70 (0.71 – 4.07)	0.228	1.65 (1.47 – 2.38)	0.007
40 to 59 years	1.49 (1.04 – 2.13)	0.029	0.94 (0.42 – 2.10)	0.887
≥ 60 years	1.99 (0.80 – 5.00)	0.139	1.08 (0.46 – 2.55)	0.855
Schooling				
> 8 years	1		1	
≤ 8 years	0.82 (0.52 – 1.31)	0.423	2.01 (1.04 – 3.89)	0.037
Clinical form				
Extrapulmonary	1		1	
Pulmonary	2.79 (1.21 – 6.43)	0.016	2.05 (0.92 – 4.60)	0.079
Alcohol abuse				
No	1		1	
Yes	1.25 (0.70 – 2.23)	0.449	1.66 (1.03 – 2.67)	0.037
Development				
Cure	1		1	
Abandonment	0.92 (0.52 – 1.61)	0.779	5.96 (4.13 – 8.60)	<0.001
Death	1.03 (0.63 – 1.69)	0.906	1.15 (0.62 – 2.15)	0.645
DRTB	1.33(0.17– 10.67)	0.787	2.54 (0.31– 20.61)	0.384

The associated factors were identified by the logistic regression model. Odds Ratio (OR). Confidence Interval (CI). Drug-Resistant Tuberculosis (DRTB).

tion of disease severity by older patients, while younger ones do not show the same stimulus, besides having lifestyle habits that hinder compliance with treatment, especially after the clinical improvement[6,25].

The pulmonary clinical form was associated with cases of relapse, in agreement with the study by Oliveira and Moreira[6] and Sahly et al.[2]. This finding may be justified by the fact that tuberculosis is the most frequent, easily diagnosed form and the main source of transmission.

As for males, there was an association with readmission after abandonment, probably because frequency of abandonment is significantly higher in males[26,27], which may be related to lifestyle habits and women being more resistant and having greater health care than men[28].

Another variable that showed an association with cases of readmission after abandonment was low schooling, which is considered a reflection of a whole set of poor socioeconomic conditions that increase vulnerability to TB and are responsible for the higher incidence of the disease and lower adherence to tuberculosis. treatment[29,30].

Alcohol abuse has been associated with readmission to treatment, which in addition to affecting the immune system contributes significantly to treatment abandonment and has been shown to be a predictor of irregular chemotherapy[17], which explains the higher percentage of alcohol abuse among the readmitted patients[25,26,31-33].

While AIDS, after adjustment, has not shown an association with cases of retreatment due to relapse of this study, it is important to highlight that literature has strongly evidenced this relationship[9,17,34], which can be explained by immunodeficiency, which facilitates exogenous reinfection and endogenous activation[2,9,35,36], in addition to treatment plans for both AIDS and TB having adverse side effects, which contributes to abandonment and consequent readmission[37].

Readmission cases were almost six times more likely to result in new treatment abandonment, in agreement with findings by Dooley

et al.[38], Ferreira et al.[26] and Silva et al.[39]. Several reasons have been attributed to this situation of non-adherence to treatment, which involve social, cultural, demographic and structural barriers of health programs[25,40,41]. These cases should be addressed as a priority group, in an attempt to avoid aggravation and development of resistant bacteria, thus requiring systematic monitoring throughout the treatment.

One of the major difficulties found in this study was the use of secondary sources, which showed a large number of variables without information or with incomplete data, which may have hindered some analyses. However, this study is relevant, since it allows knowing factors associated with one of the problems pointed out in the literature as difficulties for TB control, thus contributing with information that can be used for the planning of tuberculosis control strategies in the State of Maranhão.

Conclusion

We can conclude that the probability of relapse was higher in adults with pulmonary tuberculosis and readmission in young male adults with low education, alcohol-dependent and with greater odds of abandoning treatment again. Thus, a systematic follow-up of post-discharge tuberculosis cases, in addition to investments in education and health, can contribute to the prevention and control of the cases. It is worth mentioning that, in this context, the structuring of programs to meet this demand and the training of community workers, which serve as a bridge between health services and the community are important points that can contribute to a better control of tuberculosis.

Collaborations

TC Silva, PFS Matsuoka, DMC Aquino and AJM Caldas mentioned participated in the design and reviews that resulted in this paper.

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