

Tuberculosis Recurrence: Associated Factors in an Epidemiological Surveillance Group of São Paulo

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ABSTRACT

Analyze the factors related to cases of tuberculosis (TB) recurrence in reports of the Epidemiological Surveillance Group XXIX/São José do Rio Preto/SP. This is a case-control study that analyzes pulmonary TB reports in the period between 1996 and 2014. Cases were reports of "Recurrence" and control: reports classified as "New" case and with "Healed" outcome. Odds ratio and multivariate analysis with 95% confidence interval were used to analyze the data. The variables of gender and adverse outcome in the 7th month remained significantly associated with recurrence. Males showed 1.8 times greater risk ($p = 0.0551$) and individuals who obtained an adverse outcome in the 7th month of treatment were 4.6 times more likely to recur ($p = 0.0000$). We found two factors associated with recurrence: male gender and adverse treatment outcome, which shows the need to assess the quality of the care provided.

Descriptors: Tuberculosis; Recurrence; Therapeutics; Case-Control Studies.

INTRODUCTION

Tuberculosis (TB) is a disease recognized worldwide as a priority, because of its magnitude. In 2012, the World Health Organization (WHO) estimated 1,300,000 of deaths in the world, with Brazil being responsible for 80% of cases, listed among the 22 countries prioritized by the WHO, with the State of São Paulo being the biggest notifier⁽¹⁻³⁾.

In Brazil, one of the current strategies for disease control is a set of practices aimed at treatment adherence, reducing abandonment and raising cure rates, mainly through Directly Observed Treatment (TDO), which consists in observation, by the healthcare professional, of the patient taking the medication correctly as a way of developing a connection⁽¹⁻²⁾. The literature shows that in places with effective coverage by the TDO strategy, healing rates can reach upwards to 87%⁽⁴⁾.

However, there are obstacles to cure the disease, prolonging the period of transmissibility and causing social impact, because of the economic cost and emergence of multidrug resistance. The main complexities are the retreatment cases, be it by disease recurrence or abandonment⁽⁴⁾.

Recurrence is the appearance of the disease in its active form after completing a treatment and receiving a discharge for being cured. It can be caused by endogenous reactivation due to biological determinants, or exogenous reinfection, more frequent in endemic regions. These conditions are equal and differentiation is clinically possible only through molecular techniques, which are seldom performed since the treatment is the same in both cases^(1,4).

The bacillary reactivation is still unknown, and there are only hypotheses. It is believed that approximately 90% of infected individuals remain in a latent state; 5 to 10% progress to the disease and 5% of cured individuals presented endogenous reactivation⁽¹⁾.

Some regional studies, in Recife/PE and in Campinas/SP, showed that around 15% of reported cases per year are retreatments. It is known that a TB treatment scheme, when followed properly, is able to provide healing rates close to 100% as well as recurrence rates lower than 5%⁽⁵⁻⁶⁾. In patients who received chemotherapy properly, the chance of reactivation is more frequent in the first two years; in inverse cases, reactivation occurs a few months after discharge^(3,6-8).

The scope of non-adherence to the TB treatment is multidimensional, involving treatment (amount of medicines, long duration, and the presence of side effects), health services and the socio-cultural context, such as issues of alcoholism and drug addiction, irregular treatment factors that influence directly on abandonment, deaths and recurrences of tuberculosis⁽⁵⁻⁶⁾.

In the line of determinants for recurrences, it is believed that individuals with immune suppression, especially those with HIV/Aids and Diabetes Mellitus, had the bacillary destruction process affected, increasing the likelihood of a bacillus latency state⁽⁵⁻⁶⁾.

With the advent of HIV, the literature shows high rates of recurrence and mortality in TB/HIV-coinfected patients^(4-5,9). Mortality is twice as common in this group, not only by the degree of immune suppression but also by association with other comorbidities and the non-use of antiretroviral. Due to this scenario, the WHO recommends HIV testing for all patients with a diagnosis of TB^(4-5,8-9).

Patients who smoke are also seen as having a potential risk of recurrence. Nicotine is the substance most important in reactivation, decreasing the host's resistance and cellular changes, and increasing the risk of persistent bacteria after treatment⁽⁴⁾.

Note that the scenario of relapses is still complex, but seldom investigated, with numerous gaps to be

addressed. Despite notorious results after implantation of the PCNT, today, it is necessary to improve the strategies and look more closely at indexes that affect health care quality.

In this context, this study aimed to analyze the factors related to cases of pulmonary tuberculosis (TB) recurrence reported from 1996 to 2014 in the Epidemiological Surveillance Group XXIX/São José do Rio Preto/SP (GVE XXIX).

METHODS

Descriptive-analytical study, case-control type (1:1). We considered pulmonary TB reports from 1996 to 2014 in the Information System for Tuberculosis Patient Control in the State of São Paulo (TBWEB), in the cities that were part of the Epidemiological Surveillance Group XXIX/São José do Rio Preto/SP.

The GVE XXIX is a regional representative of the Epidemiological Surveillance Center (CVE/SP) that regulates the Epidemiological Surveillance System in the State of São Paulo. It covers 67 cities belonging to the Regional Management Committees of Catanduva, José Bonifácio, Votuporanga and São José do Rio Preto, representing one of the largest regional representatives in extension and number of cities, totaling 3% of the total number of new cases of TB in the State of São Paulo during 2010⁽¹⁰⁾.

Inclusion criteria

- **Case:** pulmonary TB reports are classified as "Recurrence", in historical series from 1996 to 2014.
- **Control:** reports were classified as "New" case and with "Healed" outcome, in historical series from 1996 to 2014.

We selected two variables that caused confusion for pairing:

- **Year:** over the years, the treatment of TB was modified (introduction of medications, professionals view of the disease and government investments).
- **Reporting city:** heterogeneities between cities (social, demographic, socio-economic) can interfere with health care. The cities were categorized according to the resident population⁽¹¹⁾ and stratification of the Brazilian Institute of Geography and Statistics (IBGE)⁽¹²⁾ into five population subgroups: zero to 4,999 inhabitants, 5,000 to 9,999, 10,000 to 19,999, 20,000 to 49,999, and greater than or equal to 50,000. When it was not possible to pair the same city, we chose another that bordered and belonged to the same classification of population category.

Exclusion criteria

Transfer of the patient to another state, change of diagnosis; city not part of the GVE 29, when pairing was not possible; duplicated reports as "New" and "Relapse", to avoid pairing between reports of the same patient, considering only the "Recurrences"; patients classified with extrapulmonary tuberculosis or mixed tuberculosis.

In the period between 1996 and 2014, there were 4,429 reports of TB cases in the Epidemiological

Surveillance Group XXIX/São José do Rio Preto/SP (GVE XXIX). After the examination of the exclusion criteria, we selected in this study 388 records classified as pulmonary TB, with 194 being considered as "cases" and 194 as "controls" (Figure 1).

We used the recurrence of TB as the dependent variable. We considered the variables in Chart 1 as the independent variables.

Chart 1: Variables selected for the study.

Variables	Categories/Comments
Gender	Female
	Male
Age group	Children: from 0 to 12 years of age
	Teenagers: from 13 to 18 years of age
	Adult: since there is no official classification, we considered individuals 19 to 59 years of age.
	Older adults: 60 years old or older.
Institutionalization	Yes: hostels, psychiatric hospitals, institutions of long permanence, penal institutes, among others.
	No
Diagnostic confirmation criteria	Epidemiological-clinical: without bacteriological confirmation, i.e. bacteriological exams, such as sputum smear microscopy or sputum culture or of other materials, were not performed and/or other exams performed had negative results for the disease.
	Bacteriological: without bacteriological confirmation, i.e. bacteriological exams, such as sputum smear microscopy or sputum culture or of other materials, were performed and the exams had positive results for the disease.
Complementary exams	Suggestive: when other tests were performed, such as x-rays, autopsy, and histopathology, among others, and had suggestive results for the disease.
	Non-suggestive: when other tests were performed, such as x-rays, autopsy, and histopathology, among others, and had non-suggestive results for the disease.
	Unknown: when there was no information on the performance of other tests or a lack of information about results of the tests carried out.
TB/HIV Co-infection	Positive
	Negative/Unknown
TB/Aids Co-infection	Yes
	No
Chemical Dependency	Yes
	No
Diabetes Mellitus	Yes
	No
Other problems associated	Mental problems and others. In the information system used, there are the item "Others" and an open field to enter the specification. In this study, we found: Hypertension, Cancer, Rheumatic Disease, Hepatitis B and C, Hypothyroidism, Epilepsy, Chronic Kidney Disease, Pulmonary Emphysema, Heart Failure, and Lupus Erythematosus.
Favorable outcome in the 7th month	Yes: Cure
	No: Death, Abandonment/Absence, In outpatient treatment/Hospitalization.
	The adverse treatment outcome does not include recurrence since recurrence is a criterion of choice to be a "Case" within the study.
Sputum smear microscopy for follow-up	Yes: when at least one sputum smear microscopy or of other material was performed during treatment.
	Yes: when a sputum smear microscopy or of other material was not performed during treatment.
Hospitalizations during treatment	Yes
	No

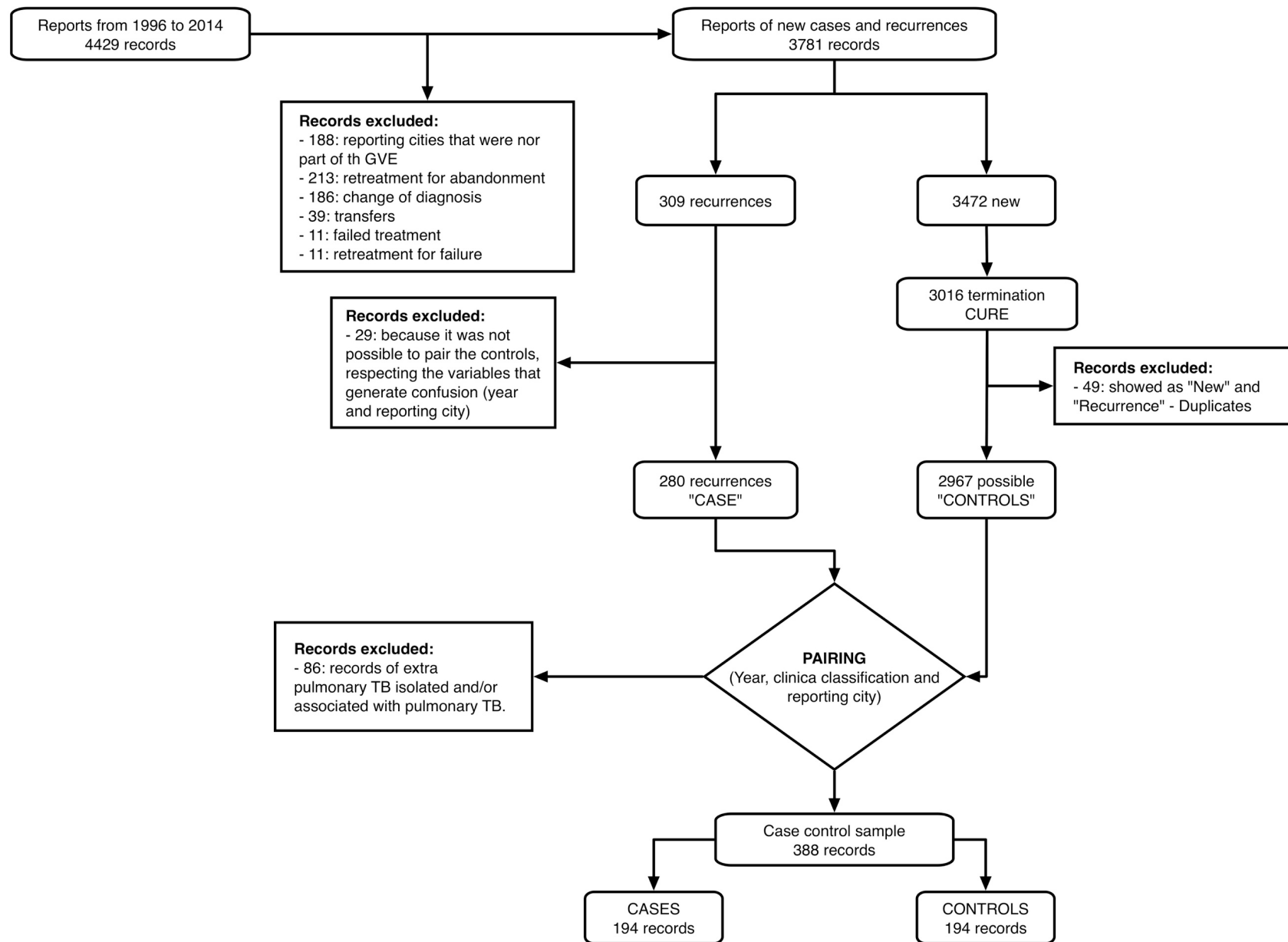


Figure 1: Schematic view of the exploratory system of information screening TBWEB, 1996 to 2014.

For data analysis, we initially used simple frequencies and gross (calculated by the ratio between the discordant pairs) odds ratio (OR), with 95% confidence interval, considering as a basic category the category of the variable whose assumption is to be of lower risk for recurrence according to theory. Later, we performed a multiple analysis through the conditional logistic regression model stepwise backward, considering the pairing adopted (year and reporting city) and obtaining the adjusted OR. We initially considered in the model the independent variables which showed significant association with the outcome in statically bivariate analysis at the 20% level ($p < 0.2$). In the multiple analysis, we adopted a significance level of 5%. Data analysis was performed on the survival package of the R Program version 3.0.2.

The project had the approval of the Research Ethics Committee of the Medical School of São José do Rio Preto, Protocol no. 73763/2012.

RESULTS

The prevalence of recurrence in relation to the total of cases in this study was around 6% (include in the calculation the method for prevalence). The gross OR showed that the variables gender, age group, associated issues, TB/HIV co-infection, chemical dependency, other associated issues, a favorable outcome in the 7th month, and hospitalizations during treatment showed statistically significant association with the outcome (recurrence of pulmonary tuberculosis) in bivariate analysis.

After adjusting the model in the multiple analysis, only the variables of gender and adverse outcome in the 7th month remained significantly associated with recurrence. Male gender presented odds 1.8 times higher than females for recurrence and was marginally significant ($p = 0.0551$). Individuals with an adverse outcome in the 7th month of treatment showed odds 5.6 times higher than those with a favorable outcome for recurrence, with $p = 0.0000$.

Table 1: Factors associated with recurrence of tuberculosis in pulmonary cases reported to the GVE 29 in bivariate analysis, São José do Rio Preto, SP, Brazil, from 1996 to 2014.

VARIABLES	Cases (n)	Controls (n)	GROSS OR	CI (95%)	p
Gender					
Male	158	140	1.857	[1.093 – 3.157]	0.0222
Female	36	54	1		
Age group					
Child/Teenager	10	3	0.3	[0.0826 – 1.09]	0.0674
Adult/Older adult	191	184	1		
Institutionalization					
Yes	6	7	1	[0.3921 – 3.471]	0.782
No	188	187	1.167		
Diagnostic confirmation criteria					
Clinical - epidemiological	52	46	1.188	[0.742 - 1.9]	0.474
Bacteriological	142	148	1		
Complementary exams					
Suggestive	152	154	0.9394	[0.5754 – 1.534]	0.803
Not suggestive/Unknown	42	40	1		
Associated Problems					
Yes	108	77	1.939	[1.274 – 2.952]	0.002
No	86	117	1		
TB/HIV Co-infection					
Positive	40	18	2.467	[1.354 – 4.494]	0.032
Negative/Unknown	154	176	1		
Chemical Dependency					
Yes	60	40	1.8	[1.104 – 2.935]	0.0185
No	134	154	1		
Diabetes Mellitus					
Yes	12	13	0.9091	[0.3861 – 2.141]	0.827
No	182	181	1		
Other problems associated					
Yes	13	7	1.857	[0.741 - 4.655]	0.187
No	181	187	1		
Favorable outcome in the 7th month					
Yes	90	156	1	[3.239 - 10.08]	0.0000
No	104	38	5.714		
Control sputum smear microscopy					
Yes	128	135	1	[0.7581 - 2.201]	0.347
No	66	59	1.292		
Hospitalization					
Yes	67	44	2.437	[1.362 - 4.362]	0.0027
No	127	150	1		

Table 2: Multiple analysis of factors associated with recurrence of tuberculosis in pulmonary cases reported to the GVE 29, São José do Rio Preto, SP, Brazil, from 1996 to 2014.

Variables	ADJUSTED ODDS	CI (95%)	P
Gender			
Male	1,8046	[0.9873 - 3.299]	0,0551
Female	1		
Favorable outcome in the 7th month			
No	5,6717	[3.2000 - 10.0520]	0,0000
Yes	1		

DISCUSSION

In the world, TB recurrences revolve around 5% per annum; in Brazil, the Ministry of Health (MS)

provides an estimate of 10% retreatments (abandonment and recurrences)⁽⁵⁾. The recurrences indicator is relevant due to its relationship with other variables, such as those related to the individual (immunity, comorbidities, age, sociodemographic) or to health services (accessibility, training of health professionals)⁽¹³⁾.

In the natural history of diseases, TB is more prevalent in men, influenced by factors related to risk exposure^(4,14). This study showed no difference, as the male gender had a greater risk of recurrence (Table 10). In regards to age group, the literature shows the range between 20 and 50 years as susceptible to TB⁽¹⁵⁾. However, with the increase in life expectancy, there have been more reports of the disease in the age group older than 60 years of age.

The gender issue is a factor that influences the onset of some diseases, as well as assistance and access to health. In countries where cultural issues predominantly advocate for men, the use of health services, as well as the indicators, is prevalent among them. TB is commonly diagnosed in men, which can be a bias, because of the gender inequality common in health care, even in Brazil⁽¹⁴⁾.

In the country, there is no inequality when it comes to the availability of services since the health system is universal. However, the fact that the hours of operation of the units are incompatible with the work schedules of most of the male population created a barrier for those who need the service, worsening the clinical condition, hindering treatment adherence, facilitating the abandonment and the reappearance of the disease, be it by new exposition to the pathogen or by reactivation of the bacillus.

The institutionalization, whether in prison regime or not (nursing homes, hostels, etc.), is something that complicates the control of the disease, facilitating the transmission and the illness⁽¹⁶⁾. Contrary to this assumption, in this study, the fact that the patient is institutionalized might be considered as a factor of protection. However, since that is a specific population, and after multiple analysis showed no statistical confirmation, this assumption cannot be sustained, requiring a separate study.

The Manual of Recommendations for TB control (2009)⁽¹⁾ defines direct sputum smear microscopy as the main method for diagnosis of the disease. For cases of suggestive clinical symptomatology, but with negative sputum smear microscopy, we recommend the culture, which is a method with high specificity and sensitivity, capable of increasing diagnostic confirmation by up to 30%⁽¹⁾.

The fact that the criteria for confirmation were epidemiological-clinical with negative bacteriological tests showed no statistical significance, as well as the fact that the additional tests had non-suggestive and/or unknown results. However, it is necessary to highlight in this result the precariousness of the active search for respiratory symptomatic cases (people with a cough for over 15 days), which is one of the pillars of disease control, and recommended as a goal, to examine 1% of the population annually⁽¹⁾.

In the state of São Paulo, the active search indicator increased from 33.6% in 2003 to 65.1% in 2011. The GVE 29 also raised their rates from 31% in 2003 to 53% in 2012⁽¹¹⁾. Despite advances, it should be noted that there is no prioritization of this exam in health services, according to national recommendations. According to the literature, the non-solicitation of the examination can occur due to failures in the operation and due to unavailability of products and/or logistics, situations that are not real in the context of the GVE

29, making possible the absence of suspicion of the disease during the clinical care⁽¹⁾.

One of the challenges for the disease control are the high rates of TB/HIV co-infection. We know that around 8.9% of individuals with TB in Brazil are coinfecting with the HIV virus. The coinfecting patient's immune response is jeopardized, which favors the development of the active disease in any phase of HIV infection (asymptomatic or acquired Immunodeficiency Syndrome (Aids)), making TB the leading cause of death in this group, with 20% death rates in co-infection^(1,4-5-7,9,16-17).

Due to the severity of the co-infection situations, one of the strategies advocated by the PNTC is HIV testing for TB patients, i.e., 100% of TB cases are expected to be tested and that antiretroviral therapy should be started early. However, the literature shows a low frequency in the realization of serology and sub-reporting suggestive data, such as filling out the field "Not done", "Ignored", or "Blank"^(1,4,16). In the GVE 29 region, the sub-reports had a decline in the historical series, going from 30.19% in the year 1996 to 8.55% in the year 2012.

It is known that chemical dependency is a predisposing factor for recurrences and that the use of illicit drugs is a challenge to public health. The context in which the addict lives is highly conducive to TB, because of the precariousness of the drug consumption locations and the high flow of people, most of them with impaired immune profile⁽⁶⁾, as well as the predisposition to abandon the treatment, be it by the context dynamic (lack of routine, biological and somatic symptoms triggered by the effects of substances, lack of perception of the disease's severity) or by the relationship with health teams, since the care of these patients requires persistence by the professionals⁽¹⁸⁾.

An effective TB treatment completion has an important influence on the non-reactivation of TB, as already stated by the literature. Among the predictors of adverse outcome at the end of the treatment (death and abandonment), Orofino (2012) highlights social issues, like alcoholism and socioeconomic factors, in addition to adverse reactions to the drug treatment and lack of understanding and knowledge about the disease⁽¹⁷⁾.

We must also consider the health services' organizational issues, the difficulty of accessibility (delay in care, schedules incompatible with the job shifts, geographic reasons) underestimating the expanded concept of health, and leaving the patient unmotivated⁽¹⁹⁾. In this study, we did not explore the issues related to the adverse outcome, but the statistical significance of this variable as a risk for recurrences was notable.

Another question to this study is the effectiveness of the monitoring of the patient in treatment, as the rate of non-solicitation of control sputum smear microscopy is high. Panjabi⁽¹⁸⁾ noted that there is a close relationship between the sputum's bacteriological state during treatment and TB recurrence, making it a risk factor for recurrences⁽¹⁸⁾. Thus, we also considered in the adverse outcome at the 7th month patients who were still in outpatient treatment and those hospitalized.

Bardout's⁽⁴⁾ study shows an elevated level of smears positivity in cases of recurrence during treatment, hypothesizing the inadequate adherence to therapy, prescription of an incorrect or inadequate treatment regimen, sub-therapeutic levels of drugs due to malabsorption or interactions, superinfection with resistant

M. tuberculosis. Treatments in experimental conditions showed the recurrence of the disease after one or two years⁽⁴⁾.

In earlier times, the criterion to be discharged from the treatment was the disappearance of symptoms, coupled with a negative smear test. Today, discharge is granted after two negative bacteriological tests, one of them at the last month of treatment, regardless of clinical symptoms⁽⁸⁾. Monthly sputum exams are recommended by MS, but when it is not possible, performing the test in the second, fourth and sixth month of treatment becomes essential⁽¹⁾.

It is known that early diagnosis, as well as strict monitoring of the treatment, can lead to a reduction of various indicators related to TB, among them the number of hospitalizations for the disease. In this study, we did not investigate the reasons for the hospitalization, and there are numerous reasons for this to happen, for example, drug intolerance and its side effects. However, it is known that TB is one of the causes listed as sensitive for outpatient care, and high rates of hospitalization suggest possible deficiencies in the quality of care, causing higher financial costs, prolonging the time of transmission of the disease and increasing the number of people infected through contact with sick individuals⁽¹⁵⁾.

Difficulties in this study that can be highlighted are: the fact that the information was gathered before the year when TBWEB was implemented, and, since we worked with secondary data, errors or a lack of reports recording is expected; it was not possible to work with all the variables that would be interesting for this study, due to lack of completeness when filling out reports; due to the wide historical series and extensive region, it was not possible to collect data from all cities, and exclusion criteria had to be used; to better study the recurrences specifically, it would be ideal to have data regarding the patient's previous treatment, but that was also not possible, since the TBWEB is for the exclusive use of the state of São Paulo and there are several patients who were previously treated in the cities of other states, and it was not possible to access these data.

CONCLUSION

This study outlined the profile of TB recurrences in the Epidemiological Surveillance Group XXIX - São José do Rio Preto/SP in order to identify related factors. We identified two variables significantly associated with recurrence: the male gender, which as 1.8 times greater risk than the female gender ($p = 0.0551$) and an adverse outcome in the 7th month of treatment, with a chance of recurrence six times higher ($p = 0.0000$).

Note that even with all the governmental and social assistance efforts to control TB, there is still much to be done. Considering that the search for new cases is insufficient and, where found and treated, there is a portion with TB recurrence, the proposal for effective control of the disease is still far from happening.

The scope of recurrence still has a long way ahead. The present study, even though it was regionalized, reveals us critics who require non-extendable resolution to be current, highlighting the deficiency of treatment operationalization, as shown by the data for diagnostic criteria and treatment outcomes. Furthermore, the social problems that leverage the negative outcomes for the disease control urge the

necessity coping and no more marginalization.

Surveillance should pay attention to the significant cases of disease recurrence and the possible associated factors and, with shared responsibility, the GVE XXIX and the cities must rethink the attention being given to cases of TB, evaluate the quality of care, and propose changes aimed at the effective control of the disease.

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