Rev Rene. 2021;22:e70733.
DOI: 10.15253/2175-6783.20212270733
www.periodicos.ufc.br/rene

Original Article

Prevalence of drug-resistant tuberculosis and associated factors*

Prevalência de tuberculose drogarresistente e fatores associados

How to cite this article:
Sousa GJB, Maranhão TA, Leitão TMJS, Moreira TMM, Souza JT, Pereira MLD. Prevalence of drug-resistant tuberculosis and associated factors. Rev Rene. 2021;22:e70733. DOI: https://doi.org/10.15253/2175-6783.20212270733

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*Extracted from the dissertation entitled "Uso do método CRISP-DM na predição do encerramento do tratamento da tuberculose como ferramenta de apoio ao cuidado", Universidade Estadual do Ceará, 2018.

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ABSTRACT

Objective: to estimate the prevalence of drug-resistant tuberculosis and associated factors. **Methods:** a retrospective study that evaluated 74,006 cases of tuberculosis registered in the Notifiable Diseases Information System. In the multivariate analysis, the outcome variable "drug resistance" was used to estimate the prevalence ratio of factors associated with drug resistance. **Results:** a rate of 0.5% of drug resistance was estimated (n=388). A higher prevalence was observed in cases classified as relapse, post-dropout re-entry, and transfer. There was a 53.0% increase when sputum smear microscopy was positive and a 6.5 increase for positive sputum culture. The opposite effect was observed when the diagnostic test for human immunodeficiency virus was not performed. **Conclusion:** a low prevalence of drug-resistant tuberculosis was estimated compared to international scenarios. The main factors associated with the disease were related to retreatments and positive sputum smear and culture results.

Descriptors: Tuberculosis; Tuberculosis, Multidrug-Resistant; Nursing; Epidemiology; Public Health.

RESUMO

Objetivo: estimar a prevalência de tuberculose drogarresistente e os fatores a ela associados. **Métodos:** estudo retrospectivo que avaliou 74.006 casos de tuberculose registrados no Sistema de Informação de Agravos de Notificação. Na análise multivariada, utilizou-se da variável desfecho "resistência medicamentosa" para estimar a razão de prevalência dos fatores associados à drogarresistência. **Resultados:** estimou-se taxa de 0,5% de drogarresistência (n=388). Observou-se maior prevalência nos casos classificados como recidiva, reingresso pós-abandono e transferência. Houve aumento de 53,0% quando a baciloscopia de escarro foi positiva e de 6,5 vezes para cultura de escarro positiva. Efeito contrário foi observado mediante a não realização do exame diagnóstico para vírus da imunodeficiência humana. **Conclusão:** estimou-se baixa prevalência de tuberculose drogarresistente comparada a cenários internacionais. Os principais fatores associados à doença estiveram ligados aos retratamentos e ao resultado positivo da baciloscopia e cultura de escarro.

Descritores: Tuberculose; Tuberculose Resistente a Múltiplos Medicamentos; Enfermagem; Epidemiologia; Saúde Pública.

Received: Apr. 8th 2021; Accepted: July 5th 2021.

Introduction

Drug-resistant tuberculosis (TB) is a growing global public health threat, with it estimated that less than 12% of drug-resistant TB cases are cured[1]. Among the types of drug resistance, rifampicin-resistant TB and multidrug-resistant TB (resistance to rifampicin and isoniazid at the same time) stand out. In addition, the most severe form is called extensively resistant TB, which occurs when the multidrug-resistant form also shows resistance to a fluoroquinolone and a second-line injectable drug[2].

Globally, 3.3% of new cases and 18% of already treated cases developed rifampicin-resistant TB or multidrug-resistant TB. As per the World Health Organization, in 2019, there were about 465,000 new cases of rifampicin-resistant TB, of which, 78% developed into multidrug-resistant TB. Moreover, the highest burden of the disease is in India (27%), China (14%) and Russia (8%)[3]. As a consequence, this form presents treatment regimens that can exceed 18 months, surpassing the standard regimen by 12 months[4-5].

It is known that diagnosis requires bacteriological confirmation, use of rapid molecular tests, and culture methods. Treatment, in addition to the use of second-line drugs, must include counseling and monitoring of adverse effects due to the use of multiple drugs concomitantly. Even with the advances observed in TB programs, data indicate that only one third of the cases of resistance underwent treatment[3]. It is noteworthy that such treatments increase health care costs, since they often involve hospitalization, as opposed to the common decentralized model[6].

Of the three lists of the 30 countries with the greatest burden of TB, Brazil is on two of them: TB infections and TB co-infections with the Human Immunodeficiency Virus (HIV). The only list that Brazil is not on is that of countries with the highest number of cases of drug-resistant TB. Even so, the World Health Organization points out that about 2% of the Brazilian cases are rifampicin resistant and less than 3% are multidrug resistant[3]. In this context, the Brazilian National Plan for TB Control proposes programmatic strategies that include case detection, adherence to treatment, contact control, and strategies aimed at populations at higher risk of developing TB, including people living with HIV, people deprived of freedom, homeless people, indigenous people, health professionals, users of alcohol and other drugs, people with diabetes mellitus, and smokers[7-8].

In this context, it is important to highlight that the literature on drug-resistant TB in Brazil is scarce. Therefore, regional differences and studies that identify associated factors are still few and far between. In Brazil, the Northeast Region, one of the most unequal in terms of human development and per capita income[9], the state of Ceará has a high incidence (32.3 cases/100,000 inhabitants) and mortality (2.4 deaths/100,000 inhabitants) for the disease[10], considered as an important state for the control of this disease in the country.

In view of the above, it is believed that it is vital and urgent to study the aspects surrounding this type of TB so that prevention strategies can be put into practice before drug-resistant TB becomes a national epidemic. Thus, we aimed to estimate the prevalence of drug-resistant tuberculosis and associated factors.

Methods

This is a retrospective, secondary database study conducted in Fortaleza, Ceará, Brazil, one of the nine states that make up the Northeast Region of Brazil. Ceará has the eighth largest population in the country, estimated at about 9.13 million inhabitants, distributed among 184 municipalities and a demographic density of 56.76 inhabitants per Km^2 (11th in the national ranking).

The data source used in this investigation was the Notifiable Diseases Information System for Tuberculosis (SINAN-TB), formed by a set of variables that are obtained through the notification form and monitoring of the disease, which are filled out by health professionals, who notify the disease, and are entered by professionals from the municipal health secretariats. The notified data from all the municipalities are

sent to the state health departments, which consolidate them, and then send them to the Ministry of Health.

The data was collected from the database that comprised all reported cases from January 2001 to December 2017, in the state of Ceará. This period was selected in order to show how the disease behaves in the 21st century until the year in which the data were available. It was adopted as an inclusion criterion the case having been notified and entered into the database and, as an exclusion criterion, it was used the non-filling of the outcome variable "closure situation". Thus, of the 75,948 cases reported, 1,942 were excluded, leaving 74,006 notifications at the end. It is noteworthy that several cases had fields with missing data, despite this, they were kept in the study, since the variables could be used in other analyses.

The following predictor variables were used: sex, age, education, race, area of residence, type of entry, form of the disease, sputum smear microscopy, sputum culture, HIV testing and Acquired Immune Deficiency Syndrome (AIDS), alcoholism and performance of supervised treatment. It is noteworthy that the variables AIDS and HIV are distinct in SINAN-TB, while the first shows the serology of the case, the second presents the results for the diagnostic test requested. Thus, they may present different results in the system used. The variable that corresponds to the antiretroviral therapy of the participant was not included in the study, because it was entered into the system only in 2015. These were chosen according to epidemiological criteria.

As the outcome variable, we chose the closure situation: drug-resistant TB. This was defined according to the criteria of the Brazilian Ministry of Health. Thus, a case was closed as drug-resistant TB when drug resistance to any drug used in the treatment of tuberculosis was confirmed by means of a susceptibility test or rapid molecular test for tuberculosis[10].

For data analysis, simple and percentage frequencies were used to verify the prevalence of each nominal predictor variable in the outcome. Then, when applying the Shapiro-Wilk test, it was found that only age did not have a normal distribution ($p<0.001$), and it was preferred to present it with the median and the interquartile range. In order to verify the association of the variables with the outcome, the Chi-square test was applied for categorical variables; and for age, the Mann-Whitney test was used. In both cases, those with $p<0.05$ were considered significant.

To calculate the Prevalence Ratio (PR) of the predictors, the Poisson regression model with robust variance was used. This model was chosen to verify the point estimate with greater reliability and to have narrower confidence intervals (95%CI). The Adjusted Prevalence Ratio (APR) was controlled for age (continuous), gender, and education, as they were understood as possible confounders of the study.

In the initial multivariate model, the independent variables that were significant in the bivariate analysis were inserted. After that, the variables with the highest p-value were removed one by one. Thus, only those variables considered statistically significant ($p<0.05$) remained in the final model. The analyses were performed in Stata 12.

Although there is no direct contact with the patients in the study, the database contains individual information of each person reported. Thus, the project was sent for ethical review to the State University of Ceará and approved according to protocol No. 2,687,046/2018. It is reiterated that at the time of database collection, the researcher, together with the Ceará State Health Department's Surveillance Center, removed any attributes that identified the participants, such as name, mother's data, and address.

Results

Of the 74,006 cases that were part of the study, a prevalence of 0.5% (n=388) of drug resistance was observed. The median age of all cases was 38 (interquartile range: 26 - 52) years and 40.5 (interquartile range: 30 - 51) years of cases with drug-resistant TB. In both sexes, 0.5% of cases showed drug resistance. It was observed that 1.0% (n=50/4,962) of the black race developed drug-resistant TB and 1.2% of indigenous individuals (n=3/254) had this form of the dise-

ase. As for education, 1.0% of those with incomplete higher education (n=5/515) and 0.9% of those with incomplete primary education I (n=34/3,679) showed drug resistance. Regarding the area of residence, 0.5% of those living in urban areas developed drug-resistant TB (n=45/10,826) (Table 1). The variables age, race/color, and education showed significant associations with drug-resistant TB (p<0.05).

Table 1 – Sociodemographic characteristics of patients with drug-resistant tuberculosis. Fortaleza, CE, Brazil, 2018

Variables	Drug-resistant tuberculosis			p*
	Total	Yes (%)	No (%)	
Age (median)	38 (26 – 52)	40,5(30–51)	38 (26 – 52)	0.040
Sex (n=73,984)				0.960
Female	27,447 (37.1)	144 (0.5)	27,303(99.5)	
Male	46,537 (62.9)	243 (0.5)	46,294(99.5)	
Race/Color (n=58,941)				<0.001
White	10,231 (17.4)	34 (0.3)	10,197(99.7)	
Black	4,962 (8.4)	50 (1.0)	4,912 (99.0)	
Yellow	726 (1.2)	3 (0.4)	723 (99.6)	
Brown	42,768 (72.6)	248 (0.6)	42,520(99.4)	
Indigenous	254 (0.4)	3 (1.2)	251 (98.8)	
Education (n=53,213)				0.020
Illiterate	9,890 (18.6)	46 (0.5)	9,844 (99.5)	
Incomplete elementary school	12,411 (23.3)	75 (0.6)	12,336(99.4)	
Complete elementary school	3,679 (6.9)	34 (0.9)	3,645 (99.1)	
Incomplete middle school	13,439 (25.3)	73 (0.5)	13,366 (99.5)	
Complete middle school	3,060 (5.7)	18 (0.6)	3,042 (99.4)	
Incomplete high school	5,110 (9.6)	23 (0.5)	5,087 (99.5)	
Complete high school	3,673 (6.9)	19 (0.5)	3,654 (99.5)	
Incomplete higher education	515 (1.0)	5 (1.0)	510 (99.0)	
Complete higher education	1,436 (2.7)	5 (0.3)	1,431 (99.7)	
Housing zone (n=71,536)				0.370
Urban	60,235 (84.2)	315 (0.5)	59,920(99.5)	
Rural	10,826 (15.1)	45 (0.4)	10,781(99.9)	
Peri-urban	475 (0.7)	2 (0.4)	473 (99.6)	

*Chi-square test

Among the main clinical and epidemiological characteristics, it was observed that 1.9% of the relapsing cases (n=93/5,028), 1.2% of the post-dropout re-entries (n=50/4,302), and 0.6% of the mixed TB cases (n=8/1,272) developed drug resistance. Of the cases that had positive sputum cultures, 2.5% (n=190/7,443) showed resistance and in those who were seropositive, 0.5% (n=21/3,953) showed this pattern. When alcoholics, drug-resistant TB was seen in 0.8% (n=79/9,414) of cases. The difference in HIV-positive and AIDS values is noteworthy, mainly due to differences in the reporting of both findings. The clinical and epidemiological variables, except for AIDS (p=0.430), were statistically significant for drug-resistant TB (p<0.05) (Table 2).

Table 2 – Clinical and laboratory characteristics of patients with drug-resistant tuberculosis. Fortaleza, CE, Brazil, 2018

Variables	Drug-resistant tuberculosis			p*
	Total	Yes (%)	No (%)	
Type of entry (n=73,944)				<0.001
New case	60,614(82.0)	210 (0.4)	60,404 (99.6)	
Relapse	5,028(6.8)	93 (1.9)	4,935 (98.1)	
Post-dropout re-entry	4,302 (5.8)	50 (1.2)	4,252 (98.8)	
Doesn't know	843 (1.1)	5 (0.6)	838 (99.4)	
Transfer	3,157 (4.3)	30 (1.0)	3,127 (99.0)	
Disease form (n=73,988)				<0.001
Pulmonary	64,524 (87.2)	364 (0.6)	64,160 (99.4)	
Extrapulmonary	8,192 (11.1)	16 (0.2)	8,176 (99.8)	
Mixed	1,272 (1.7)	8 (0.6)	1,264 (99.4)	
Sputum smear microscopy (n=73,988)				<0.001
Positive	43,539 (58.8)	285 (0.7)	43,254 (99.3)	
Negative	14,495 (15.6)	43 (0.3)	14,452 (99.7)	
Not performed	15,364 (20.8)	50 (0.3)	15,314 (99.7)	
Not applicable	590 (0.8)	10 (1.7)	580 (98.3)	
Sputum culture (n=73,988)				<0.001
Positive	7,443 (10.1)	190 (2.5)	7,253 (97.5)	
Negative	4,036 (5.5)	19 (0.5)	4,017 (99.5)	
Not realized	2,466 (3.3)	16 (0.6)	2,450 (99.4)	
Not performed	60,043 (81.1)	163 (0.3)	59,880 (99.7)	
Human Immunodeficiency Virus (n=74,005)				<0.001
Positive	3,953 (5.3)	21 (0.5)	3,932 (99.5)	
Negative	26,233 (35.5)	221 (0.8)	26,012 (99.2)	
Ongoing	2,549 (3.4)	12 (0.5)	2,537 (99.5)	
Not realized	41,270 (55.8)	134 (0.3)	41,136 (99.7)	
Acquired Immunodeficiency Syndrome (n=40,787)				0.430
Yes	3,428 (8.4)	19 (0.6)	3,409 (99.4)	
No	37,359 (91.6)	250 (0.7)	37,109 (99.3)	
Alcoholism (n=46,531)				0.004
Yes	9,414 (20.2)	79 (0.8)	9,335 (99.2)	
No	3,117 (79.8)	215 (0.6)	36,902 (99.4)	
Supervised treatment (n=54,789)				0.012
Yes	33,630 (55.3)	178 (0.5)	33,452 (99.5)	
No	27,159 (44.7)	106 (0.4)	27,053 (99.6)	

*Chi-square test

Variables that showed p<0.20 in the bivariate tests were entered into an initial multivariate model, which was adjusted for age (continuous), gender, and education. In the final model, higher prevalence of drug-resistant TB was observed when the case is reported as relapse (PR=4.66; CI: 3.61-6.00), post-dropout re-entry (PR=2.38; 95% CI: 1.69-3.34) and transfer (PR: 2.35; 95% CI: 1.61-3.44). In addition, there was a 53.0% increase in resistance when sputum smear microscopy was positive (95%CI: 1.13-2.08), and a 6.5% increase when sputum culture was positive (95%CI: 5.22-8.11). An intriguing result was found for the HIV test, where a 45.0% (95% CI: 0.44-0.70) reduction in resistance was identified when it was not performed. Furthermore, it was found that when adjusted, disease forms, alcoholism, and supervised treatment lost their respective effects (Table 3).

Table 3 – Robust Poisson regression model adjusted for age (continuous), sex and education to estimate the prevalence ratios of factors associated with drug-resistant tuberculosis. Fortaleza, CE, Brazil, 2018

Variabled	Initial model	p*	Final model	p*
	PR (95%)		APR (IC95%)	
Type of entry				
New case	1	-	1	-
Recurrence	5.29(4.15–6.73)	<0.001	4.66 (3.61 – 6.00)	<0.001
Post-dropout re-entry	3.32(2.44–4.51)	<0.001	2.38 (1.69 – 3.34)	<0.001
Transfer	2.71(1.86–3.97)	<0.001	2.35 (1.61 – 3.44)	<0.001
Disease form				
Pulmonary	1	-	-	-
Extrapulmonary	0.34(0.21–0.57)	<0.001	-	-
Mixed	1.11 (0.55–2.24)	0.760	-	-
Sputum Bacilloscopy				
Positive	1.86(1.39–2.50)	<0.001	1.53 (1.13 – 2.08)	0.006
Negative	1	-	1	-
Not performed	0.93 0.63–1.36)	0.697	1.12 (0.74 – 1.70)	0.585
Sputum culture				
Positive	8.98(7.34–11.0)	<0.001	6.50 (5.22 – 8.11)	<0.001
Negative	1	-	1	-
Not performed	2.28(1.37–3.80)	0.001	2.41 (1.44 – 4.04)	0.001
Human Immunodeficiency Virus				
Positive	0.63(0.40–0.98)	0.043	0.76 (0.49 – 1.17)	0.214
Negative	1	-	1	-
In Progress	0.55(0.31–0.99)	0.049	0.65 (0.34 – 1.23)	0.183
Not performed	0.38(0.31– .74)	<0.001	0.55 (0.44 – 0.70)	<0.001
Alcoholism	1.44(1.12–1.87)	0.005	-	-
Supervised treatment	1.35(1.07–1.72)	0.013	-	-

*p-value referring to robust Poisson regression; PR: Prevalence Ratio; APR: Adjusted Prevalence Ratio; 95%CI: 95% Confidence Interval

Discussion

The main limitation of this research is in the use of secondary data from the tuberculosis notification forms, because several variables were not completely filled out and could not be used in the study. Also, it is limited to inferring only associations and not causality. Another limitation is that the analysis was conducted considering only the state of Ceará, which may prevent generalizations to other contexts. The change in the form in 2014 may have caused underestimation of the true prevalence of the disease. Finally, the temporal cut-off until 2017 may make it difficult to identify the real prevalence of drug-resistant TB. However, the theme studied and the number of notifications and years used support the results of the research.

This study shows the factors associated with forms resistant to standard medication for the treatment of the disease. Thus, it is understood that the disease occurs in a cyclical manner, because the individual uses antibiotics that eliminate a large portion of the bacilli and, when the treatment is suspended, new microorganisms grow. Thus, this cycle favors the mutation of the bacteria, generating new resistant strains[11].

Although the prevalence of resistance found in this study is low, international studies show countries with different realities from Brazil. For example, in Pakistan, it was estimated that 11.5% of cases presented at least some type of drug resistance[12], which shows a reality about 20 times greater than that of Ceará. In corroborating these findings, mathematical models of epidemiological estimation indicate that cases of multidrug-resistant TB and extensively resistant TB tend to grow over the years, even with programmatic actions of case management with adherence to treatment and medication[13]. Thus, it is understood that the problem permeates determinants that go beyond the biological or institutional, other factors may be related to the increase of drug-resistant TB in the world.

In addition, one of the most important findings

of this study was that forms of entry other than new cases (relapses) significantly contribute to the presentation of resistant forms of TB. Similarly, a study conducted in the Southeast Region of Brazil found that relapse increases the chances of resistance by 7.72 times and post-relapse reentry by 3.91 times[14].

Thus, the importance of monitoring the treatment of the disease is emphasized, especially at the time of medication administration. In this sense, the directly observed treatment is pointed out as a fundamental strategy, in order to reduce the risk of resistance and increase the possibility of cure. Along with it, counseling, health education, and distribution of incentives are pointed out as factors that influence adherence to treatment[15].

Thus, adherence or loss of follow-up of patients undergoing treatment for drug-resistant TB occurs through the medications (duration of treatment, its adverse effects, number of medications and pain caused by injectables), the services (conflict between work and treatment centers, behavior of professionals, insufficient counseling and access), socioeconomic factors (stigma, scarce family and social support, unemployment and financial problems) and the patient himself (little awareness of his health status, myths about the disease, alcoholism and problems of confidentiality)[16]. Therefore, follow-up programs should also aim at strengthening the approach beyond the pharmacological one.

Other strategies can also be used in the short, medium and long term. Short-term strategies include increasing the supply of susceptibility testing with accurate diagnosis of resistant forms and prevention measures such as vaccination and treatment of latent TB infection. In the medium and long term, the development of new diagnostic tests and less toxic drugs is needed to enable treatments that are shorter and more effective[1,17]. In addition, the importance of partnerships with the private sector is highlighted, in order to determine the real magnitude of the disease and reduce the possible biases that data from public services may present[18].

Regarding diagnostic tests, we identified divergence between the findings of this study and those found in the literature regarding the relationship between HIV and the risk of drug-resistant TB[19]. On a global scale, this relationship remains inconsistent[20]. It can be assumed that testing is being performed only on persons entering as new cases or that people who develop drug-resistant TB already have known serological status. Among other explanations, it is believed that this variable is causing confusion or interaction between variables. In any case, we emphasize the importance of TB-HIV co-infection for public health and the importance of the test.

In addition, a systematic review showed that people with TB-HIV may experience fewer adverse effects than people with TB alone. This statement was justified because of the higher mortality rates among people who are co-infected, and there is not enough time for any adverse effects to appear. However, when a person is newly diagnosed with HIV, the risk of experiencing adverse effects is increased[20].

Conclusion

This study estimated a lower prevalence of drug-resistant tuberculosis in Ceará than the national average and that of other countries. Factors associated with the increased prevalence of this event were identified, mainly linked to retreatments and positive results of sputum smear microscopy and culture. Therefore, measures that support treatment with daily use of medications, tracking of possible failures, adequate social support, and timely testing are vital to break the line of bacterial resistance.

Acknowledgments

To the *Fundação Cearense de Apoio ao Desenvolvimento Científico e Tecnológico* (Cearense Foundation for the Support of Scientific and Technological Development), for granting the master's scholarship to George Jó Bezerra Sousa.

Collaborations

Sousa GJB, Maranhão TA and Pereira MLD contributed to the conception, study design, analysis, data interpretation and writing of the article. Leitão TMJS, Moreira TMM, and Souza JT collaborated with relevant critical review of the intellectual content. All authors cooperated for the final approval of the version to be published.

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