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ORIGINAL ARTICLE

IMPACT OF THE COVID-19 PANDEMIC ON TUBERCULOSIS DIAGNOSIS IN THE GENERAL POPULATION AND THE PRISON POPULATION IN MANAUS, AMAZONAS

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Highlights:
(1) Covid-19 delayed tuberculosis diagnosis in the general population. (2) Activescreening reduced tuberculosis cases in prison population. (3) Isoniazid showed highest resistance in both populations.

ABSTRACT

Introduction: During the pandemic, health services were restructured to meet the demand from COVID-19 cases, which led to the neglect of other diseases, including tuberculosis (TB). *Objective:* Assess whether there was a change in the number of TB cases identified using the rapid molecular test for tuberculosis and whether there was an increase in resistance to antituberculosis drugs after the pandemic, both in the general population and the prison population. *Methodology:* Individuals who underwent molecular rapid testing for tuberculosis (MRT-TB) and sensitivity tests to anti-TB drugs were evaluated at the Northern District Municipal Laboratory, during the period from January 2018 to December 2022. *Results:* We included 12,208 (81.7%) individuals from the general population and 2,731 (18.3%) from the prison population (PP) of the city of Manaus. The initial year of the pandemic, 2020, had the highest percentage of positive tests (20.6%, n=205) in the general population. This trend continued in the following years, being equal to 12.5% (n=347) and 12.9% (n=392), in 2021 and 2022, respectively. However, in the PP, the years with the highest rates of positive exams were 2018 and 2019, with 13.1% (n=55) and 20.5% (n=50) respectively, with a significant reduction in the percentage of positive exams in later years. Resistance to the drug Isoniazid was the most frequent resistance found in both the general population and the prison population, but without a significant increase. *Conclusion:* The Covid-19 pandemic negatively influenced the control of tuberculosis, increasing the number of cases of this disease in the general population, and it is necessary to improve health policies to control and reduce cases of this disease.

Keywords: social isolation; covid-19; pulmonary tuberculosis; drug resistance.

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INTRODUCTION

Tuberculosis (TB) is an infectious disease transmitted by the bacillus *Mycobacterium tuberculosis* (MTb) and, until 2019, was one of the main causes of death due to infectious disease in the world.[1] The state of Amazonas, especially the capital Manaus, has the highest number of TB cases in Brazil, with 84.1 cases per 100,000 inhabitants, and continues to be a major challenge for health authorities.[2]

As of 2020, with the spread of the Covid-19 pandemic across several countries, the causative virus, known as Sars-CoV2, emerged as the leading cause of death in the world. The pandemic brought about significant changes in people's lives. One of them was the adoption of social distancing measures, which lead to families staying at home for long periods, with the aim of reducing the spread of the Covid-19 virus.[3] In the context of TB in the city of Manaus, this recommendation may have facilitated transmission by individuals with bacilliferous TB in isolation with other people/family members. Added to this was the difficulty in accessing TB diagnosis and treatment in health facilities, due to the fact that they were focused on coping with the Covid-19 pandemic.[4,5]

Another relevant aspect that the pandemic brought was the increased use of various antibiotics during COVID-19 infections, both by medical prescribers and by the general population, through self-medication, the latter often being stimulated by fake news that was spread on the internet.[6,7] The indiscriminate use of these medications, such as antibiotics and immunosuppressants, may possibly have influenced the virulence of MTb, making it more resistant.[8-10]

One population that is particularly vulnerable to the transmission of infectious diseases, in particular TB, is the prison population (PP). This vulnerability can be explained due to infrastructure issues, such as overcrowding in cells and inadequate ventilation, as well as malnutrition, illiteracy and smoking.[11,12]

Given the above, this study aims to evaluate the impact of the Covid-19 pandemic on the increase in the number of TB cases in the general population and in the prison population in Manaus, as well as observe whether there was an increase after the pandemic in resistance to first-line drugs used in TB treatment.

METHODOLOGY

This is a retrospective, observational, descriptive and analytical study of sputum exam results of patients with suspected TB. Individuals from the general population and the PP, who entered the Bacteriology sector of the North District Municipal Laboratory in Manaus, with a medical request for laboratory diagnosis of TB, during the period from January 2018 to December 2022 were evaluated.

The North District Municipal Laboratory is responsible for conducting laboratory tests of clinical samples of the entire northern sector of Manaus, one of the most populous areas of the city. Patients are treated in the basic health units, by doctors or nurses, and are sent with the request to perform the tests in the laboratory. In addition to the basic health units, the laboratory receives biological samples, including sputum, from five prison units, located at Km 8 on the BR 174 highway.

All the sputum samples from individuals over 18 years of age, of either sex, were selected. Individuals with incomplete or antagonistic registration data were excluded.

The epidemiological characteristics (sex, age and new case/retreatment) and the results of the molecular rapid test for tuberculosis (MRT-TB) were collected using SoftLab, which is the software used by the laboratory network in Manaus. The results of the sensitivity test, which is performed by Lacen-AM, were collected using the GAL program (laboratory environment manager), which is a program of the Brazilian Ministry of Health, used nationally for routine laboratory monitoring.

The MRT-TB was used for the detection of the IS1081-IS6110 gene of the MTb bacillus using the Gene Xpert system (Cepheid, USA), which performs a polymerase chain reaction (PCR) technique in real time. Results indicative of "traces" were not included in the study and were designated as indeterminate. The evaluation of drug resistance was evaluated via two methodologies: 1) detection of mutations of the rpoB gene, which indicate resistance to Rifampicin, which is also done via MRT-TB; 2) results of sensitivity tests performed when MTb culture growth occurs, which indicates the sensitivity to the four first-line drugs used in the treatment of tuberculosis (Rifampicin, Isoniazid, Streptomycin and Ethambutol).[13]

Analyses of results and individualized statistics of the general population and the prison population were carried out. Analysis of descriptive and exploratory data was performed using IBM SPSS Statistics (version 22.0). To verify the normality of the data in both groups, the Shapiro-Wilk test was used. For data without normal distribution, the Mann-Whitney test was used. The relationships between the diagnosis obtained through the MRT-TB and the year of occurrence were verified using Pearson's chi-square test, as well as the presence of resistance to anti-tuberculosis drugs in both populations. The significance level of 5% was used.

The study complied with the recommendations of Resolution 466/2012 of the National Health Council, which regulates human research in Brazil. The study plan was submitted to the Ethics Committee of the Amazonas State University, through the Platforma Brasil, and approved under certificate of presentation for ethical assessment (CAAE) Nº 56619422.7.0000.5016, opinion Nº 5,285,424.

RESULTS

Characterization of the study populations

A total of 14,939 tests were included, these being 12,208 (81.7%) individuals from the general population and 2,731 (18.3%) individuals from the PP of the city of Manaus, capital of the state of Amazonas, which were carried out between the years 2018 and 2022. In 2020, there was the lowest inclusion of individuals for testing for TB in the general population, corresponding to the initial year of the pandemic. In the PP, the lowest inclusion of individuals was in 2019, before the pandemic period. After this decline in 2019 and 2020, the number of examinations in the two populations continued to increase in the subsequent years (Table 1).

In the general population, of the 12,208 examinations, 6,245 (51.2%) were for females and 5,963 (48.8%) were for males. In the prison population, of the 2,731 exams, only 73 (2.7%) refer to females, while 2,658 (97.3%) refer to males (Table 1).

As for the age group, in the general population, the highest frequencies are in the age groups 19 to 29 and 40 to 49, which correspond respectively to 2,686 (22.0%) and 2,312 (18.9%) and make up 40.9% of this population. In the PP, 1,617 (59.2%) tests were performed on individuals aged between 19 and 29 (Table 1).

Regarding the type of case, for the general population, 11,290 (92.5%) are new cases, while in the prison population, 2,566 (94.0%) refer to the same group of cases (Table 1).

Table 1 – Frequency of examinations per year and the epidemiological characteristics of the general population and the prison population

CHARACTERISTIC	General population		Prison population	
	n (12,208)	%	n (2,731)	%
Year				
2018	2,536	20.8	421	15.4
2019	2,854	23.4	244	8.9
2020	996	8.2	581	21.3
2021	2,775	22.7	715	26.2
2022	3,047	25.0	770	28.2
Sex				
Female	6,245	51.2	73	2.7
Male	5,963	48.8	2.658	97.3
Age group				
19 - 29	2,686	22.0	1.617	59.2
30 - 39	2,077	17.0	811	29.7
40 - 49	2,312	18.9	218	8.0
50 - 59	2,110	17.3	54	2.0
60 - 69	1,788	14.6	28	1.0
70 and over	1,235	10.1	3	0.1
Type of case				
New case	11,290	92.5	2,566	94.0
Retreatment	918	7.5	165	6.0

Source: Elaborated by the authors.

Laboratory profile of detection results from MRT-TB

In the five-year period analyzed, 1,387 (11.4%) MRT-TB tests were positive in the general population, while in the PP, MTb detection occurred in 242 (8.9%) tests.

In the general population, the initial year of the pandemic (2020) had the highest percentage of positive tests 20.6% (n=205). The percentages of positive tests in the following years (2021 and 2022) continued to be higher than before the pandemic, being equal to 12.5% (n=347) and 12.9% (n=392), respectively, showing that the frequencies of these positive results were significantly higher (p<0.0001; Figure 1A). In contrast, in the PP, the years with the highest rates of positive tests were 2018 and 2019, with 13.1% (n=55) and 20.5% (n=50), respectively, with a significant reduction in the percentage of positive tests in later years (p<0.0001; Figure 1B).

Figure 1 – Number of tests evaluated for the detection of tuberculosis by MRT-TB and positivity rate in the general population (A) and in the prison population (B), before and during the COVID-19 pandemic.

Source: Elaborated by the authors — *p-value < 0.0001* Pearson's chi-square test

Source: Elaborated by the authors — *p-value < 0.0001* Pearson's chi-square test

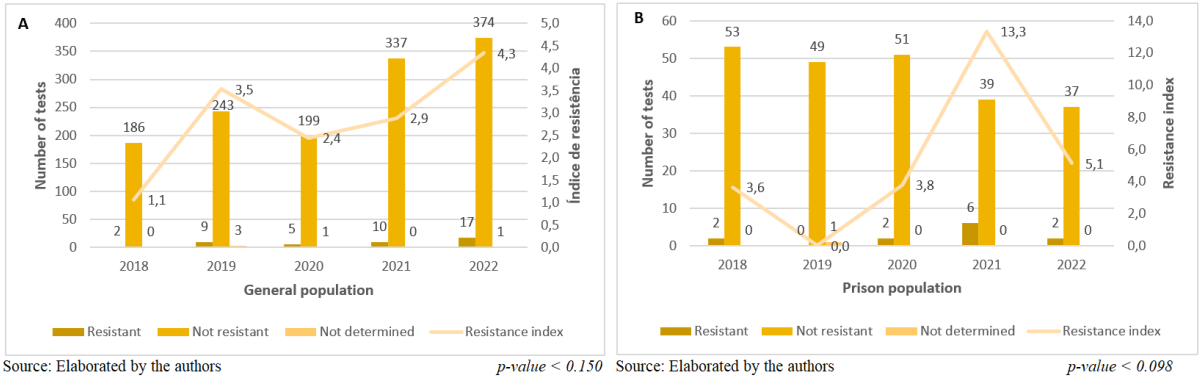
Figure 1 – Number of tests evaluated for the detection of tuberculosis by MRT-TB and positivity rate in the general population (A) and in the prison population (B), before and during the COVID-19 pandemic.

Results for detection of resistance to Rifampicin using MRT-TB

Regarding the evaluation of Rifampicin resistance using MRT-TB, in the general population, 43 (3.1%) tests showed resistance. In the PP, 12 (5.0%) tests indicated drug resistance.

It is observed that in the general population there is an increase in the number of tests that indicate resistance over the five years, but this increase is not accompanied by the resistance index and has no statistical significance (p=0.150) (Figure 2A).

In the PP, only in 2021 (n=6, 13.3%) was the number of tests indicating resistance to Rifampicin higher than in other years (before and after the Covid-19 pandemic); however, this difference did not show statistical significance (*p*=0.098; Figure 2B).



Source: Elaborated by the authors — *p-value < 0.150* Pearson's chi-square test

Source: Elaborated by the authors — *p-value < 0.098* Pearson's chi-square test

Figure 2 – Number of MRT-TB test results evaluated for Rifampicin resistance and the resistance index in the general population (A) and in the prison population (B), before and during the COVID-19 pandemic

Test results for sensitivity to antituberculosis drugs

In the general population, the frequency of tests that showed resistance to antituberculosis drugs were: 18 (2.7%) to Rifampicin; 58 (8.8%) to Isoniazid; and 21 (3.3%) to Streptomycin (Table 2). In the PP, the results showed the following frequencies: four (3.8%) for Rifampicin; five (4.8%) for Isoniazid; one (1.0%) for Ethambutol; and four (3.9%) for Streptomycin (Table 3). Therefore, in the two populations studied, Isoniazid represented the majority of cases of resistance.

Table 2 – Relationship between resistance to antituberculosis drugs in the general population before and during the Covid-19 pandemic

Drug	Resistant		Sensitive	Total	*p**
Rifampicin	**n (18)**	**Resistance index (%)**	**n (644)**	**662**	
2018	2	1.5	128	130	
2019	4	11.4	31	35	
2020	5	3.4	142	147	*0.019**
2021	4	2.2	177	181	
2022	3	1.8	166	169	
Isoniazid	**n (58)**	**Resistance index (%)**	**n (604)**	**662**	
2018	11	8.5	119	130	
2019	2	5.7	33	35	
2020	10	6.8	137	147	*0.657*
2021	16	8.8	165	181	
2022	19	11.2	150	169	
Ethambutol	**n (0)**	**Resistance index (%)**	**n (636)**	**636**	
2018	0	0.0	130	130	
2019	0	0.0	35	35	
2020	0	0.0	143	143	*NA*
2021	0	0.0	181	181	
2022	0	0.0	147	147	
Streptomycin	**n (21)**	**Resistance index (%)**	**n (615)**	**636**	
2018	5	3.8	125	130	
2019	0	0,0	35	35	
2020	5	3,5	138	143	*0.855*
2021	6	3,3	175	181	
2022	5	3,4	142	147	

NA: Not applicable
* Significant at p<0.05 (5%) Pearson's chi-square test
Source: Elaborated by the authors.

In the general population, the analysis of the results of the sensitivity tests to antituberculosis drugs revealed only the presence of samples resistant to Rifampicin (p=0.019). Despite this result, it cannot be said that the total number of cases of resistance to this drug has increased due to the Covid-19 pandemic (Table 2).

As for the PP, according to Table 3, the analysis of cases of resistance to drugs against TB did not reveal significant resistance to any of the drugs (p>0.05).

Table 3 – Relationship between resistance to antituberculosis drugs in the prison population before and during the Covid-19 pandemic

Drug	Resistant		Sensitive	Total	*p**
Rifampicin	**n (4)**	**Resistance index (%)**	**n (100)**	**104**	
2018	0	0.0	38	38	
2019	0	0.0	6	6	
2020	1	3.8	25	26	*0.202*
2021	2	14.3	12	14	
2022	1	5.0	19	20	
Isoniazid	**n (5)**	**Resistance index (%)**	**n (99)**	**104**	
2018	2	5.3	36	38	
2019	1	16.7	5	6	
2020	1	3.8	25	26	*0.623*
2021	0	0.0	14	14	
2022	1	5.0	19	20	
Ethambutol	**n (1)**	**Resistance index (%)**	**n (102)**	**103**	
2018	0	0.0	38	38	
2019	0	0.0	6	6	
2020	0	0.0	26	26	*0.347*
2021	0	0.0	14	14	
2022	1	5.3	18	19	
Streptomycin	**n (4)**	**Resistance index (%)**	**n (99)**	**103**	
2018	2	5.3	36	38	
2019	0	0,0	6	6	
2020	1	3,8	25	26	*0.808*
2021	1	7,1	13	14	
2022	0	0,0	19	19	

* Significant at p<0.05 (5%) Pearson's chi-square test

Source: Elaborated by the authors

DISCUSSION

The main finding of the present study was the significant increase in the number of cases of TB detected during the Covid-19 pandemic (in the years 2020, 2021, 2022) in the general population. However, this same result was not observed in the PP, for which there was a decrease in the rate of positive TB tests over the years analyzed.

The year 2020, the beginning of the pandemic, was the year with the lowest number of TB tests in the general population, but with the highest positivity rate (20.6%). These data suggest greater

selectivity of requests, referring individuals with respiratory symptomatic profiles more compatible with TB. The following years (2021 and 2022) show the "rebound effect", where there is an increase in the demand for TB tests that was higher than in the years before the pandemic. This same trend is also observed in other Brazilian states (Sergipe, Pernambuco, Paraíba, Mato Grosso do Sul and Maranhão) and in other regions of the world (Southeast Asia, Eastern Mediterranean, Western Pacific and some other countries in the Americas).[1,2] In addition, mandatory social distancing during Covid-19, the difficulty and decrease in TB health care, increased poverty and poor diet may be other factors that contributed to this increase in the number of TB cases after the pandemic.[14-16]

In contrast, the present study shows a decrease in the rate of positive tests over the years in the PP. In 2019, the drop in the number of samples sent to perform the MRT-TB was probably due to the rebellions that occurred in prisons and the change in the management that manages the penitentiary complex.[17,18] As of 2020, an increase in the number of samples sent to the laboratory is observed; however, the rate of positive tests has decreased. Unlike the general population, for which the demand for tests is mostly spontaneous, in the prison there is an active search for respiratory symptoms, which forces the individual to perform tests for TB. With the onset of the pandemic, this search intensified, leading to an increase in the number of samples being sent for testing in the laboratory. Once TB is detected, this individual is isolated for treatment, which is fundamental for breaking the chain of transmission. Although other studies have observed a decrease in the number of TB cases in the PP, they attribute the decrease in detected cases to probable underreporting in the prison population, which is accompanied by a lack of health policies for the care of detainees.[2,19,20]

Regarding resistance to the antimicrobials used in the treatment of TB, despite the increase in the number of tests showing resistance to Rifampicin detected by MRT-TB in the general population, there was no significant increase in the resistance index. While, in the PP, no increase in this number of individuals with resistance was observed. When assessing the resistance to first-line antibiotics, Isoniazid was found to be the most resistant drug in the two populations studied. The data in the literature show an increase in Rifampicin resistance after the pandemic, but it is not possible to state that there was an increase in overall resistance because of the Covid-19 pandemic.[2,21] In these studies, it is possible to note that in the year 2020 there is a decrease in cases of resistance and that in later years the cases are close to the years before the pandemic. In 2019, we observed a decrease in drug sensitivity tests, due to the lack of inputs for culture, which may have compromised the quality of the data.

It is important to emphasize that both the WHO and the Brazilian Ministry of Health have dedicated efforts and investments to fill this gap caused by the pandemic.[22-23] In Brazil, the increase in the number of individuals tested, the expansion of preventive treatment, the strengthening of the laboratory network and the inclusion of new technologies that allow shorter treatment times are part of actions aimed at reducing TB cases by 2030.[23-24]

FINAL REMARKS

The Covid-19 pandemic had a significant impact on tuberculosis cases worldwide, exacerbating already existing challenges in diagnosing and treating this disease. The focus of health resources on dealing with the coronavirus, coupled with social distancing measures and disruptions in health services, led to a decrease in demand for the diagnosis and treatment of tuberculosis.[15,16,25] The results obtained in the present study demonstrate an increase in the number of TB cases in the general population, despite a decrease in cases in the PP, after the onset of the Covid-19 pandemic. In this context, it is extremely important to intensify the active search for respiratory symptomatic individuals for early detection of cases, develop public policies that increase surveillance for this disease, and

implement effective prevention strategies in an attempt to reduce the impact that the pandemic caused, thereby preventing the number of new cases and, consequently, deaths from tuberculosis from increasing even more.

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