

Original Article

## Tuberculosis/HIV co-infection in Northeastern Brazil: Prevalence trends, spatial distribution, and associated factors

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### Abstract

**Introduction:** The objective was to analyze the prevalence trend, spatial distribution, and TB-HIV co-infection-associated factors in an endemic scenario for TB in Northeastern Brazil.

**Methods:** An ecological and temporal series study was conducted based on secondary data obtained from the Brazilian Notifiable Diseases Information System between January 2008 and December 2019. The prevalence rates were determined for each year and the average for the period. Prais-Winsten regressions were used for temporal variation analysis, scanning techniques were used to detect spatial clusters, and the Poisson regression model was used to explore the factors associated with the outcome.

**Results:** A total of 947 TB cases were reported, of which 501 (52.9%) underwent HIV testing, and of these, 73 were positive. The average prevalence was 20.0%, ranging from 1.5% in 2018 to 44.4% in 2009. A decreasing trend was found. Sixty-seven cases (92%) were geocoded, and two statistically significant ( $p < 0.005$ ) high relative risk (RR) spatial clusters were detected. Statistically significant associations ( $p < 0.05$ ) between the co-infection and variables such as male gender, living in the urban area, entry due to relapse, and case closure due to loss to follow-up were evidenced, and these variables constituted risk factors.

**Conclusions:** A decreasing prevalence of TB-HIV co-infection has been found, as well as a heterogeneous spatial distribution with the formation of spatial clusters in urban areas characterized by socio-spatial inequalities associated with clinical-epidemiological factors. Such findings provide subsidies for rethinking health care activities and improving public policies for vulnerable populations.

**Key words:** Tuberculosis; HIV infections; comorbidity; epidemiology; spatial analysis.

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### Introduction

Tuberculosis (TB) remains a global health threat, and, since 2007, it has been considered one of the top 10 causes of death caused by a single infectious agent, accounting for 1.4 million deaths in 2019, including 208,000 among human immunodeficiency virus (HIV)-positive persons [1]. Brazil occupies the 20th position in the list of the 30 priority countries for TB and the 19th in the list of the 30 priority countries for TB-HIV co-infection, with TB being the first cause of death among patients with acquired immunodeficiency syndrome (AIDS) [2].

People living with HIV have a greater risk of acquiring TB and progressing to active disease, 26

times greater risk of developing active TB globally, and 28 times greater risk of developing active TB in Brazil [3]. This close relationship changes the perspective of controlling TB globally and increases the incidence and mortality of both diseases [3] since TB-HIV co-infection increases the risk of treatment failure, TB multidrug resistance, and relapses [4].

Scientific investigations on the morbidity and mortality from TB-HIV co-infection have been stimulated [5], as these studies are essential tools for detecting failures in health systems and services [6-9]. Investigating these infections makes it possible to identify the sociodemographic and clinical-epidemiological profiles of the affected persons and

allows additional analyses of associated factors [9], trend analysis and spatial distribution [7], and intensifying case surveillance actions subsidizing improvements in patient care [6].

Additionally, information on the spatial and temporal diffusion of TB-HIV is imperative to understand the co-infection dynamics by pointing out susceptible areas, local characteristics, and social conditions. The above elements, combined with the understanding of cultural and environmental conditions, allow the stratification of social risks [6,8].

Since TB-HIV co-infection is a social problem, it should be studied from a focal point of view, according to the spatial distribution approach. In this sense, space has been studied and understood as a reflection of society, constituting an intrinsic determinant of the population's living conditions and a category of analysis in studying social inequities in health [6,10].

Studies on the spatial analysis of TB-HIV co-infection carried out in the last decade portrayed the mortality [8,11,12] and the incidence of cases [10,13] on the African continent, as well as the prevalence of the co-infection in European countries [14,15] and Asia [16]. In Brazil, investigations were also carried out exploring the incidence [6,17], prevalence [18,19], and mortality of TB-HIV co-infection [7]. Another study has investigated the combined co-infection incidence and prevalence indicators [20]. However, no study in this regard has been carried out in Imperatriz, Maranhão, Brazil, one of the eight priority cities for TB control [21].

Studies in scenarios with a population greater than 100,000 inhabitants may reflect the epidemiological

findings of morbidity and mortality from TB-HIV co-infection and its socioeconomic conditions, which may be associated with structural deficiencies and the inability to meet the monitoring demands [6,7].

Considering the geo-epidemiological aspects presented above and the need for specific strategies and interventions that prioritize resources for vulnerable groups, this study aimed to analyze the prevalence trend, spatial distribution, and TB-HIV co-infection associated factors in an endemic scenario for TB in Northeastern Brazil.

## Methods

### *Study design*

An ecological [22] and time series [23] study was carried out based on secondary data collected from the Health Surveillance Service (HSS) of the Regional Health Management Unit of Imperatriz (UGRSI in Portuguese), from the TB notification forms of the Notifiable Diseases Information System (SINAN in Portuguese).

### *Study area*

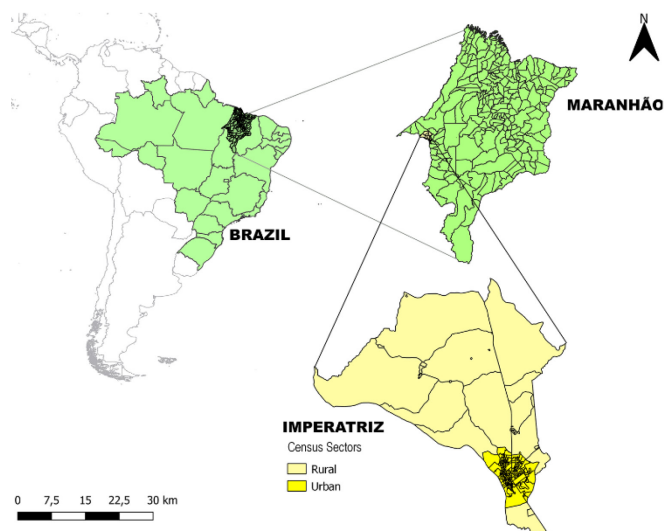
The research was carried out in the municipality of Imperatriz, located in the west of Maranhão, in Northeastern Brazil (Figure 1), where the headquarters of UGRSI is located. The city has a territorial area of 1,368,988 km<sup>2</sup> and an estimated population of 259,337 inhabitants [24]. The above population is considered the second largest in the state, and, as the city is considered a regional hub, it receives a large population from other municipalities in Maranhão and other Brazilian states, in addition to standing out as an important economic center, especially in the provision of goods and services [25].

Imperatriz has a life expectancy rate at birth of 70.9 years, a human development index (HDI) of 0.73, an incidence of poverty of 55.28%, and a Gini coefficient of 0.46 [24]. The city is part of a scenario characterized by precarious socioeconomic and operational indicators for TB [26]. Imperatriz is divided into 246 census sectors, 218 in the urban area and 28 in the rural area [27], distributed in 160 neighborhoods [25].

### *Data sources*

TB cases reported between January 1, 2008, and December 31, 2019, were surveyed, including TB cases that underwent HIV testing. TB cases with anti-HIV not performed or "in progress" were excluded. The sociodemographic and clinical-epidemiological variables selected from the individual TB notification form were age group, gender, race, education, complete

**Figure 1.** Map of Brazil, highlighting the state of Maranhão and the census tracts of the city of Imperatriz, Maranhão.



address, area of residence, mode of entry into the surveillance system, clinical form, sputum smear, sputum culture, histopathology, case closure, and HIV testing. The data collection occurred in February 2020 after authorization from the HSS through a pre-coded form containing the variables of interest.

*Data analysis*

The prevalence of TB-HIV co-infection for each year investigated was obtained by calculating the ratio between the number of TB cases with a positive HIV test and the number of TB cases who took the HIV test, as done previously in other studies [28, 29]. The prevalence rates were summed and then divided by 12 to estimate the average prevalence rate of TB-HIV.

Prais-Winsten regressions were used for trend analysis, considering the autocorrelation in time series, determining the annual rate of change (ARC) in percentage, and their respective confidence intervals [30]. Based on these parameters, ARC was classified as increasing, stable, or decreasing, with the non-significant *p*-value resulting in a stability trend (accepting the null hypothesis that the prevalence rate has not changed over the years). Significant *p*-values result in the classification of an upward trend (positive ARC) or a decreasing trend (negative ARC).

The geocoding process was conducted using the TerraView software version 4.2.2, using the cartographic base of the municipality. The addresses of cases residing in urban and rural areas were standardized and matched with the cartographic base of the municipality, with UTM/WGS84 projection available in the .shp (shapefile) format. The linear interpolation of the complete addresses took place at a

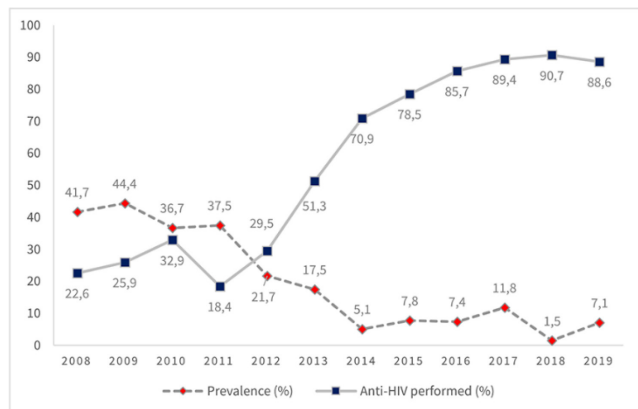
point in the corresponding street segments, making it possible to elaborate patterns of event points.

The Batch Geocode tool (available at <http://batchgeo.com/br/>) was used to record cases of TB-HIV co-infection not located in the cartographic base. The tool mentioned above searches Google Earth for coordinates. Then, the geocoded cases were spatially distributed in the respective census sectors (ecological units of analysis in this study).

The spatial scan analysis was adopted using the discrete Poisson model to detect spatial clusters, establishing criteria such as the non-overlapping of clusters, the maximum cluster size of 50% of the exposed population, and 999 replications [31]. This analysis was processed using the SaTScan 9.3 software, taking into account the distribution of TB-HIV co-infection cases according to population, age group, and gender of the census tracts and identifying statistically significant clusters (*p* < 0.005) of high and low relative risks.

A descriptive analysis of sociodemographic and clinical-epidemiological variables was performed concerning the outcome (HIV testing) to identify factors associated with TB-HIV co-infection. Poisson regression models with robust variance adjustment were used [32]. Sociodemographic and clinical-epidemiological variables that presented *p* ≤ 0.20 were included in the adjusted model. The prevalence ratios (PR) and respective 95% confidence intervals were estimated directly by the regression coefficients of the model. On this occasion, the skipped data was deleted. All data were tabulated in an Excel 2019 spreadsheet, and tests were performed in IBM Statistical Package for Social Sciences (SPSS) version 24.0 at a 5% significance level.

**Figure 2.** HIV tests performed and prevalence of TB-HIV co-infection. Imperatriz (MA), Brazil (2008-2019).



Data	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	Total
TB cases	106	104	91	87	78	78	55	65	63	66	75	79	947
HIV tests performed	24	27	30	16	23	40	39	51	54	59	68	70	501
TB-HIV co-infected persons	10	12	11	6	5	7	2	4	4	7	1	5	73

*Ethical approval*

The Research Ethics Committee of the Federal University of Maranhão (UFMA) granted ethical approval for the study under opinion no. 2,159,911/2017.

**Results**

In the period between January 2008 and December 2019, in Imperatriz, 947 cases of TB were registered in SINAN, of which 394 (41.6%) did not take the HIV test, 52 (5.5%) had the HIV test result registered as "in progress", and 501 (52.9%) took the test; of these, 73 were positive.

The rate of HIV testing ranged from 18.4 to 90.7% among reported TB cases.

**Table 1.** Trend in the prevalence of TB-HIV coinfection. Imperatriz (MA), Brazil (2008-2019).

Time course	Annual rate of change (%)	95%CI		R <sup>2</sup>	p-value*	Situation
		Inferior limit	Superior limit			
2008-2019	-35.9%	-48.3	-20.6	0.7	0.001	Descending

\*Prais-Winsten regression ( $p < 0.05$ ); 95% CI: 95% confidence interval; R<sup>2</sup>: coefficient of determination.

**Table 2.** Sociodemographic and clinical-epidemiological characteristics of TB cases, according to the anti-HIV test. Imperatriz (MA), Brazil (2008 to 2019).

Variable	TB cases	
	Anti-HIV test	
	Negative n = 428 (%)	Positive n = 73 (%)
<b>Age (years)</b>		
≤ 19	29 (6.8)	4 (5.5)
20-39	189 (44.1)	44 (60.3)
40-59	133 (31.1)	16 (21.9)
≥ 60	77 (18.0)	9 (12.3)
<b>Gender</b>		
Male	268 (62.6)	56 (76.7)
Female	160 (37.4)	17 (23.3)
<b>Color/race</b>		
Mixed	298 (69.6)	44 (60.3)
Non-mixed	130 (30.4)	29 (39.7)
<b>Education (years)</b>		
≤ 8	210 (49.1)	45 (61.6)
> 8	181 (42.3)	28 (38.4)
Not informed	37 (8.6)	0 (0.0)
<b>Zone of residence</b>		
Urban	424 (99.1)	70 (95.9)
Rural	4 (0.9)	3 (4.1)
<b>Input type</b>		
New case	376 (87.9)	61 (83.5)
Relapse	16 (3.7)	10 (13.7)
Re-entry after abandonment	6 (1.4)	1 (1.4)
Transfer	30 (7.0)	1 (1.4)
<b>Clinical form</b>		
Pulmonary	381 (89.0)	62 (84.9)
Extrapulmonary	40 (9.3)	10 (13.7)
Pulmonary + extrapulmonary	7 (1.7)	1 (1.4)
<b>Smear test result</b>		
Positive	205 (47.9)	24 (32.9)
Negative	134 (31.3)	16 (21.9)
Not performed	89 (20.8)	33 (45.2)
<b>Sputum culture result</b>		
Positive	10 (2.3)	1 (1.4)
Negative	26 (6.1)	7 (9.6)
In progress	0 (0.0)	2 (2.8)
Not performed	392 (91.6)	63 (86.2)
<b>Histopathological result</b>		
Positive	12 (2.8)	2 (2.8)
Suggestive of TB	23 (5.4)	6 (8.2)
Not suggestive of TB	1 (0.2)	0 (0.0)
In progress	7 (1.7)	2 (2.8)
Not performed	385 (89.9)	63 (86.2)
<b>Case closure</b>		
Cure	396 (92.5)	52 (71.2)
Loss to follow-up	10 (2.3)	2 (2.8)
Death caused by TB	2 (0.5)	1 (1.4)
Death from other causes	7 (1.7)	11 (15.1)
Transfer	9 (2.0)	5 (6.7)
Diagnostic change	2 (0.5)	2 (2.8)
MDR TB	2 (0.5)	0 (0.0)

Results expressed by n (%); TB: Tuberculosis; MDR TB: Multidrug-Resistant Tuberculosis.

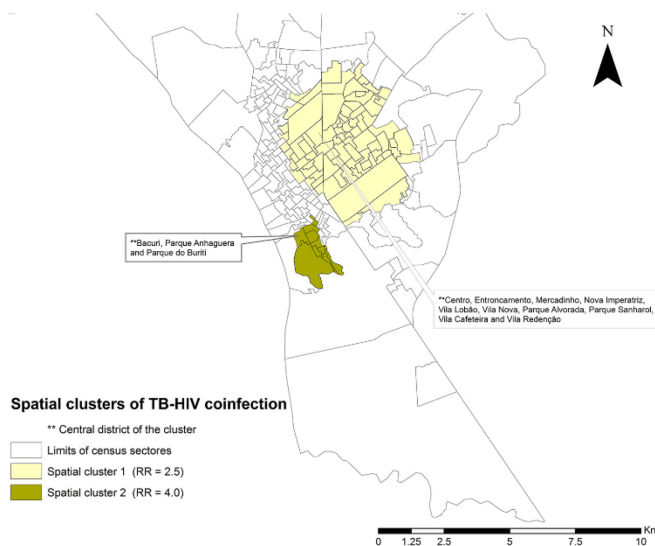
The average prevalence was 20%, ranging from 1.5% in 2018 to 44.4% in 2009 (Figure 2). Figure 2 also shows the number of TB-infected and TB-HIV-infected individuals and HIV tests performed over the period investigated.

There was a significant downward trend in the prevalence of TB-HIV co-infection over the years ( $p = 0.001$ ), with a decreasing ARC equal to  $-35.9\%$  (95% confidence interval:  $-48.3$ ;  $-20.6$ ) and  $R^2 = 0.7$  (Table 1).

Regarding the geocoding process, of the 73 cases of TB-HIV co-infection, 67 cases were geocoded (92%), restricted to the urban area of the municipality. Of these, 61 (91%) were geocoded using TerraView and six (9%) using the *Batch Geocode* tool. Even with the geocoding strategies used, six (8%) cases were not located due to inconsistencies in the addresses informed.

Two statistically significant ( $p < 0.005$ ) high relative risk spatial clusters controlled by the population of the census tracts and their distribution by gender and age were detected (Figure 3). Spatial cluster 1 ( $p = 0.002$ ) covered 40 cases of co-infection, a population of 80,614 inhabitants, and had an RR of 2.5 (95% CI 1.6-3.8), linked to 82 census sectors in the districts Centro, Entroncamento, Mercadinho, Nova Imperatriz, Vila Lobão, Vila Nova, Parque Alvorada, Parque Sanharol, Vila Cafeteira, and Vila Redenção. Spatial cluster 2 ( $p < 0.001$ ) involved six cases in a population of 9,085 inhabitants and had an RR of 4.0 (95% CI 2.5-5.6),

**Figure 3.** Map of spatial clusters of TB-HIV co-infection cases, controlled by the population of the census tracts and their distribution by gender and age. Imperatriz (MA), Brazil (2008-2019).



RR: relative risk.

limited to ten census sectors belonging to the neighborhoods of Bacuri, Parque Anhaguera, and Parque do Buriti.

The sociodemographic and clinical-epidemiological characteristics of TB cases according to the HIV test are shown in Table 2. Most TB cases with a positive HIV test were found among males, aged between 20 and 39, of mixed color/race, with less than 8 years of education, residents of the urban area, new cases, patients with pulmonary TB, who had undergone sputum culture, who had not been tested by histopathology, and patients who had been cured of TB. In addition, a greater proportion of cases had not undergone smear microscopy.

The significant associations ( $p \leq 0.20$ ) for TB-HIV co-infection identified in the crude analysis were male gender, education  $\leq 8$  years, living in the urban area, entry due to relapse, and case closure due to loss to follow-up. In the adjusted analysis, male gender (PR = 1.94; 95% CI: 1.69-2.34), living in the urban area (PR = 2.97; 95% CI: 1.49-6.99), entry due to relapse (PR = 2.90; 95% CI: 1.46-5.86) and case closure due to loss to follow-up (PR = 10.29; 95% CI: 6.63-15.98) remained associated with TB-HIV co-infection ( $p < 0.05$ ). No protective factors were identified in the crude nor the adjusted analysis (Table 3).

## Discussion

The Brazilian National Tuberculosis Control Plan, in compliance with the World Health Organization (WHO), recommends carrying out an HIV test for all TB patients, those with signs and symptoms of TB, and partners of TB-HIV patients, considering that reliable reporting of coinfecting individuals is essential for adequate disease control and comprehensive patient care [3]. However, the diagnosis of TB-HIV is usually late due to failure of the reference services [1,18,33].

HIV testing in patients diagnosed with TB is carried out heterogeneously in Brazil. HIV testing rates range from 62.4% to 92.5%, even with the high availability of diagnostic tests and a decentralized HIV infection control program [3]. The present study has shown that there has been an increase in the rate of HIV testing in TB patients, mainly from 2012 onwards, reaching approximately 90% at the end of the period studied. This finding is above the national average of 77.8% and the Maranhão State average of 84%. However, it is below the percentage found in São Luís, the capital city, of 95% in 2017 - the highest percentage of HIV tests conducted in the Brazilian capitals [34].

We highlight the improvement in HIV testing coverage due to the decentralization of HIV diagnosis

carried out by the Municipal Program for Sexually Transmitted Diseases in Imperatriz since 2009. Despite this progress, the results also raise the need for more efforts by health professionals and managers so that all patients can access adequate TB-HIV diagnosis and treatment. Actions such as extending the working hours of health units and offering rapid HIV testing are

important to minimize delays in HIV diagnosis in patients with TB [17,35].

The average prevalence of TB-HIV co-infection in the investigated period was 20%, and, as well as the prevalence rates detected from 2008 to 2013 and in 2017, it was above the average of other scenarios such as the European (4.9 %) [15], the North American (6%)

**Table 3.** Crude and adjusted analysis of factors associated with TB-HIV coinfection. Imperatriz (MA), Brazil (2008 to 2019).

Variable	TB-HIV coinfection (n = 73)			
	Gross PR (95% CI)	p-value	Adjusted PR (95% CI)	p-value
<b>Age (years)</b>				
≤ 19	1			
20-39	1.56 (0.60-4.05)	0.83	-	-
40-59	0.89 (0.32-2.48)	0.26	-	-
≥ 60	0.86 (0.29-2.61)	0.27	-	-
<b>Gender</b>				
Female	1		1	
Male	1.76 (1.55-2.02)	0.02*	1.94 (1.69-2.34)	0.03**
<b>Color/Race</b>				
Mixed	1			
Non-mixed	1.18 (0.69-2.00)	0.54	-	-
<b>Education (years)</b>				
> 8	1		1	
≤ 8	1.76 (1.01-2.17)	0.10*	1.33 (0.89-1.99)	0.08
<b>Zone of residence</b>				
Rural	1		1	
Urban	3.02 (1.25-6.71)	0.01*	2.97 (1.49-6.99)	0.006*
<b>Input type</b>				
New case	1		1	
Relapse	2.76 (1.61-4.72)	< 0.001*	2.90 (1.46-5.86)	0.005**
Re-entry after abandonment	1.02 (0.76-3.38)	0.98	1.06 (0.85-3.39)	0.69
Transfer	1.08 (0.89-3.61)	0.23	1.10 (0.92-3.89)	0.33
<b>Clinical form</b>				
Pulmonary	1			
Extrapulmonary	1.42 (0.78-2.61)	0.24	-	-
Pulmonary + extrapulmonary	0.89 (0.14-5.67)	0.91	-	-
<b>Smear test result</b>				
Positive	1			
Negative	1.01 (0.56-1.85)	0.98	-	-
Not performed	1.58 (0.89-2.96)	0.45	-	-
<b>Sputum culture result</b>				
Positive	1			
Negative	1.33 (0.52-2.32)	0.40	-	-
In progress	1.78 (0.71-2.69)	0.31	-	-
Not performed	1.52 (0.63-2.49)	0.66	-	-
<b>Histopathological result</b>				
Positive	1			
Suggestive of TB	1.45 (0.33-6.28)	0.62	-	-
Not suggestive of TB	***	-	-	***
In progress	1.55 (0.26-9.15)	0.63	-	-
Not performed	0.98 (0.27-3.62)	0.98	-	-
<b>Case closure</b>				
Cure	1		1	
Loss to follow up	8.62 (6.67-11.12)	< 0.001*	10.29 (6.63-15.98)	< 0.001**
Death caused by TB	2.87 (0.57-6.52)	0.25	2.39 (0.45-5.73)	0.18
Death from other causes	3.27 (0.92-7.24)	0.23	3.49 (0.94-7.70)	0.25
Transfer	2.28 (0.74-5.70)	0.22	2.22 (0.86-5.75)	0.27
Diagnostic change	***	-	-	***
MDR TB	***	-	-	***

\*p value < 0.20, Statistical significance; \*\*p value < 0.05, Statistical significance; \*\*\*Presence of zeroed values make it impossible to calculate the PR; PR: prevalence ratio; MDR TB: Multidrug-Resistant Tuberculosis; 95% CI: 95% confidence interval.

[36] and the Brazilian (9.5%) [33]. Such variations may occur due to differences in the calculations adopted in each study and a substantial variation in the number of TB-HIV cases due to underreporting [18]. This epidemiological indicator's knowledge is of fundamental importance, as TB-HIV is related to the increase in contagion, treatment expenses, morbidity, mortality, and drug resistance [28].

The statistically significant downward trend for TB-HIV co-infection detected in this study followed the global and national declines observed over the last decades [1]. Moreover, it may be associated with improved access to early diagnosis of HIV and the institution of ART [5,16,33]. Despite this, it remains far from the goal agreed by the WHO, which proposed the eradication of TB by 2035 [37], and the UNAIDS 90-90-90 target for ending the AIDS epidemic by 2030 [38].

Regarding the spatial analysis, specifically on the geocoding of TB-HIV cases, the percentage obtained (92%) was considered satisfactory given the use of secondary data and the incompleteness of records regarding the address of patients, as this is not a mandatory field. Inconsistencies in the information provided by the patients and non-completion of forms by the health care staff compromise the data quality [39].

It is noteworthy that the use of spatial analysis techniques enables the dialogue between local geographic and epidemiological statistics with the dynamic aspects of the population, such as migratory processes, population flow, and socioeconomic conditions [40]. In this investigation, spatial scan analysis allowed to segment the municipality into high-risk areas from the visualization of spatial clusters and demarcation of homogeneous areas for TB-HIV co-infection in census sectors of the municipality, especially in centralized regions (cluster 1), with longer occupation and high population density [25].

Census sectors belonging to the Centro neighborhood, their adjacent Mercadinho and Nova Imperatriz, and their expansion to peripheral areas, such as Vila Lobão, Vila Nova, Parque Alvorada, Parque Sanharol, Vila Cafeteira, and Vila Redenção, made up the spatial cluster 1. Although these locations have coverage for HIV testing due to the decentralization of HIV diagnosis by the Municipal Coordination of STD/AIDS/Viral Hepatitis, the target of 100% coverage in TB patients has not yet been achieved.

The expansive localities belonging to spatial cluster 1 were historically built from irregular settlements with precarious housing conditions, no sewage system, and

urban agglomeration, a space characterized by socio-spatial inequalities, often neglected by public administrations [25,41]. Such findings are consistent with other studies on spatial analysis of TB-HIV co-infection carried out in the American continent, specifically in Brazil [6,18,19], Africa [13], and Europe [14].

Added to this is the fact that a greater concentration of people favors the circulation of *M. tuberculosis* [6], and the scenario under investigation presents several areas dedicated to retail trade, represented by fairs and free markets, characterized by a high population concentration and an intense flow of people from different locations.

People residing in census tracts belonging to the Bacuri neighborhood stood out in the composition of spatial cluster 2, being four times more likely to be coinfecting with TB-HIV. The above neighborhood is one of the oldest locations in the southwest of the municipality. Most of its territorial extension results from residential effluent in a disorderly way, suffering from the presence of areas that serve only as a receiver of waste released by local inhabitants. In addition, people in the Bacuri neighborhood experience problems caused by floods due to the overflow of the Bacuri stream, especially in periods of rain, favoring the incidence of TB [25,41].

Similar structural problems are also faced in Parque Anhanguera, and Parque do Buriti neighborhoods, in spatial cluster 2, related to the accumulation of waste and the overflow of the Cacau and Capivara streams [25]. The neighborhoods mentioned above were expanded without prior planning, resulting in areas that lack essential public services and are affected by the spread of infectious diseases [41].

It is also important to mention that territorial inequalities are evidenced when considering access to health services [6]. In 2018, for example, only 60.99% of the municipality's territory was covered by the Brazilian Family Health Strategy [42]. This situation may have contributed to the underreporting of cases and raises questions about whether these areas are being assisted through spatial analysis, how this assistance occurs, and how the lack of access to health care services affects the control and surveillance of TB-HIV co-infection.

In this investigation, the cases of co-infection came from the notification of TB. It is worth noting that the greater number of cases in less-favored areas, the greater the screening of symptomatic persons for early detection aiming at early treatment, cure, and termination of the chain of transmission [2]. In addition,

the marked social inequality in Brazil, revealed by problems such as lack of access to health care resources, education, income, and basic sanitation, is closely related to the risk of becoming ill with TB-HIV [5,6].

An integrative literature review that analyzed the epidemiological aspects of TB-HIV in Brazil revealed that the prevalence of this co-infection was associated with male gender, mixed color/race, low level of education, living in urban areas, and age between 20 and 59 years [43]. The above results corroborate our findings and are associated with the epidemiological profile described in recent investigations [6,9,17,33,34].

Regarding associated factors, the male gender was significantly associated with TB-HIV co-infection, confirming that the prevalence of contagion in males follows the trend of co-infection dissemination, which tends to infect about twice the men [20]. Although not investigated in our sample, this finding may be related to poor health-related self-care and a more active lifestyle among men, increasing the exposure to risk factors such as tobacco smoke, alcohol use, and illicit drug consumption [5,43]. Other factors such as organizational conditions, inflexibility in service hours, or even underdiagnosis in women may also be involved [18]. The higher prevalence of TB in males also indicates a higher risk of HIV infection [5,18].

The urban residential area predominated in this study (95.9%) and was associated with TB-HIV co-infection similar to what was observed in prior studies [6,16,17,33]. In Imperatriz, residents in the urban area were almost three times more likely to be co-infected. This relationship suggests that a more active lifestyle, greater agglomeration in urban spaces, and increased urbanization potentiate the perpetuation of both diseases [5,6].

We have also detected a significant association between TB-HIV co-infection and entry due to relapse. This fact may be related to the intense immune compromise since the HIV infection weakens the immune system making patients up to 50 times more vulnerable to TB [1]. In addition, the therapeutic protocol for TB-HIV co-infection has a high number of drugs and adverse effects, hindering patient adherence and, consequently, favoring the selection of resistant mycobacteria, contributing to relapse [5,28]. People with HIV/AIDS exposed to *Mycobacterium tuberculosis* in places with a high prevalence of TB are strongly susceptible to acute primary TB or exogenous reinfection [1].

Another factor that was associated with TB-HIV co-infection was treatment abandonment. Coinfected

patients were about ten times more likely to drop out of treatment than anti-HIV-negative patients. Treatment abandonment, one of the main obstacles and a challenge in the fight against the disease, has been a serious problem among TB-HIV coinfecting individuals with direct consequences, including increased cost of treatment, mortality, and relapse rates, in addition to facilitating the development of resistant TB strains [1,3]. In addition, non-acceptance of the diagnosis, low socioeconomic level, low education, and prejudice contribute to treatment abandonment [5,43]. Our findings are consistent with a qualitative study conducted in the northern region of Brazil, in which the authors have shown that TB-HIV favors TB treatment abandonment, either due to the treatment itself or lack of motivation related to the imminence of death [44].

The drugs used to treat TB and HIV are free of charge through the Brazilian SUS public health system. Despite the above fact being a good strategy, it is believed that it may contribute to treatment abandonment in the scenario under investigation as some patients rely on sufficient accessibility to medications. Associated with this, factors such as drug dosage and side effects contribute to non-adherence and, consequently, facilitate abandonment. However, operational and longitudinal studies are needed to understand and elucidate the above associations.

The following limitations have been identified: (1) the underreporting of cases due to HIV testing inferior to 100% of TB cases, (2) the incomplete filling of the notification forms, and (3) the delayed update of the information system, proven by the existence of HIV tests still in progress, which has also been reported in prior studies in Brazil [7,17-20] and other countries [14,16,36].

Authors have highlighted the need for integrated work between TB and HIV services and the training of staff responsible for filling in the notification forms and feeding the health information systems, which is vital for better monitoring the patients [5,14,28]. In this way, the organizational implementation and maintenance of fast and resolute surveillance and information system are key to the good performance of TB-HIV control and monitoring strategies [17,35].

Intrinsic to ecological studies, the ecological fallacy is highlighted as a limitation of this study, considering that a phenomenon observed at an aggregate level does not necessarily imply that this same existing relationship remains at the individual level [22]. Moreover, it appears that the elimination of TB-HIV is not restricted to the health sector, depending on intersectoral management and robust investments in



housing, transport, and food. Also, intersectoriality is one of the main measures in facing social problems in the territories, emphasizing the integration of knowledge, the mobilization of resources from different sectors, and the social responsibility of the different segments of society [9,17].

Furthermore, studies determining a probabilistic relationship between the SINAN-TB and SINAN-AIDS databases should be carried out to estimate the actual prevalence of TB-HIV, given that this relationship constitutes an important tool to reduce underreporting, helping in the control of the two endemics and the improvement of disease notification databases [45].

## Conclusions

A downward trend was observed in the number of cases of TB-HIV in Imperatriz, Brazil, as well as a heterogeneous spatial distribution with the formation of urban spatial clusters characterized by socio-spatial inequalities. The co-infection was related to the male gender, living in the urban area, entry due to relapse, and case closure due to loss to follow-up.

The above findings may assist decision-making by management and healthcare stakeholders, providing subsidies for health surveillance based on the establishment of more efficient preventive and control measures, especially concerning the audacious goal launched by the WHO of a 95% reduction in TB deaths associated or not with HIV by 2035.

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## Authors' Contributions

LFSS and MSN conceived the study. MSN provided supervision for the study development. All authors were involved in the implementation of the study. FSS, GGSS, JSML, and CRAAR extracted data from the Information System. PHVC, MY, RAA, IGF, HLP, and LHS performed the statistical analysis. LMP, ACPJC, LSS, and MAAOS analyzed the data. LFSS and MSN wrote the manuscript's initial draft. All authors reviewed and edited the manuscript draft. All authors reviewed and approved the final version of the manuscript to be published.

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