The impact of the SARS-CoV-2 pandemic on tuberculosis notifications and deaths in the state of São Paulo, Brazil: a cross-sectional study

Marina Cristina Blume,[a] Eliseu Alves Waldman,[b] Ana Angélica Bulcão Portela Lindoso,[c] Maria Josefa Penón Rújula,[c] Giovanna Maria Orlandi,[c] Maria de Lourdes Viude Oliveira,[c] and Ana Marcia Sá Guimarães[a,*]

[a]Laboratory of Applied Research in Mycobacteria, Department of Microbiology, Institute of Biomedical Sciences, University of São Paulo, Brazil
[b]Department of Epidemiology, College of Public Health, University of São Paulo, Brazil
[c]Tuberculosis Division, Center for Epidemiologic Vigilance "Prof Alexandre Vranjac", São Paulo State Secretariat of Health, Brazil

The Lancet Regional Health - Americas 2024;34: 100765
Published Online xxx
https://doi.org/10.1016/j.lana.2024.100765

Summary

Background The state of São Paulo reports the highest number of tuberculosis cases in Brazil. We aimed to analyze the SARS-CoV-2 pandemic's impact on tuberculosis notifications and identify factors associated with reduced notifications and tuberculosis deaths in 2020–2021.

Methods This retrospective cross-sectional study analyzed data from 126,649 patients with tuberculosis notified in São Paulo from 2016 to 2021. Interrupted time series analysis assessed the pandemic's impact on notifications. Descriptive statistics and logistic regressions identified factors associated with decreased tuberculosis notifications and deaths during the pandemic (2020–2021) compared to the pre-pandemic period (2019).

Findings Tuberculosis notifications decreased by 10% and 8% in 2020 and 2021, respectively, with declines 2–3 times higher among individuals with no education or deprived of liberty. Contrastingly, tuberculosis notifications increased 68% among corrections workers in 2021. Diagnostics and contact tracing were compromised. Individuals with HIV, drug addiction, or deprived of liberty had lower odds of notification during the pandemic. Black and Pardo individuals or those with diabetes, treatment interruption history, or treatment changes post-adverse events had higher odds of notification. However, adverse events and tuberculosis-diabetes cases have been increasing since 2016. During the pandemic, tuberculosis-related deaths rose 5.0%–12.7%. Risk factors for mortality remained similar to 2019, with Pardo ethnicity, drug addiction and re-treatment post-adverse events emerging as risk factors in 2020/2021.

Interpretation The pandemic affected tuberculosis notifications and deaths differently among populations, exacerbating inequalities. Treatment interruption, loss of follow-up, and challenges in accessing healthcare led to increased mortality.

Funding FAPESP, CNPq and CAPES, Brazil.

Copyright © 2024 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Keywords: Tuberculosis notifications; COVID-19; SARS-CoV-2; Pandemic; Tuberculosis deaths

Introduction

The SARS-CoV-2 pandemic hampered the control of several other diseases worldwide. The reallocation of resources to fight the viral pandemic, lockdown periods, and the strain on health systems disrupted healthcare access and services.[1] These led to an overall decrease in diagnostics, treatment and prevention of many diseases, including tuberculosis.[2] Before the emergence of COVID-19, tuberculosis was the number one infectious killer in the world, but mortality rates were decreasing. Unfortunately, during the first pandemic years (2020 and 2021), mortality due to tuberculosis increased for the first time in a decade.[3] An estimated 1.6 million people died of tuberculosis in 2021, up from 1.4 million in 2019. The progress made towards the goal of 35% reduction in mortality as part of the End TB strategy was reversed.[3] Case notifications were also affected globally, decreasing by 18% in 2020 compared to 2019, with only partial recovery in 2021.[3]

*Corresponding author. 1374 Prof Lineu Prestes Avenue, Room 229, São Paulo, 05508-000, SP, Brazil.
E-mail address: anamarcia@usp.br (A.M.S. Guimarães).

Research in context

Evidence before this study

We searched PubMed, Google Scholar, and medRxiv for research articles reporting on the impact of the SARS-CoV-2 pandemic on tuberculosis notifications and deaths in Brazil or in the state of São Paulo. The following search terms were used ("tuberculosis" OR "tuberculosis notifications" OR "tuberculosis deaths") AND ("COVID-19" OR "SARS-CoV-2" OR "pandemic") AND ("Brazil" OR "São Paulo"). This search was limited to research articles, without language limitation, published from January 1st, 2020, to December 31st, 2023. Twelve studies were identified, none of which comprehensively analyzed the impact of the pandemic on tuberculosis control in the state of São Paulo. In addition, most studies were focused on tuberculosis notifications, with few analyzing a reduced set of patient-associated variables or other epidemiological indicators. Therefore, it is unclear whether the pandemic had varying effects on different population groups. Identifying the most affected groups and worst performing indicators of tuberculosis control programs will support the development of targeted policies to recover from the effects of the pandemic on tuberculosis control worldwide.

Added value of this study

Findings of this study emphasize how the pandemic exacerbated existing social inequalities among the most vulnerable individuals to tuberculosis. The SARS-CoV-2 pandemic decreased notifications in the São Paulo by 8–10%. The decline was more significant among the most vulnerable individuals, such as people deprived of liberty and those with no education. Importantly, the decline in tuberculosis notifications among people deprived of liberty was accompanied by an important increase of tuberculosis cases among corrections workers. The reporting of diagnostic tests was compromised. While cure rates decreased, treatment abandonment and loss of follow-up increased during the pandemic. Adverse events due to treatment and tuberculosis-diabetes cases have been increasing since 2016, with little effect from the pandemic. Deaths from tuberculosis increased 5 and 13% in 2020 and 2021, respectively, with changes in risk factors, including drug addiction, which is likely a consequence of increased social vulnerability of the susceptible population.

Implications of all the available evidence

Results from this study have been made available to the state tuberculosis control program to support the development of targeted-public policies to improve case finding and notifications among the most socially vulnerable individuals, and to address the issue related to the increasing numbers of adverse events due to treatment and the tuberculosis-diabetes syndemic.

Brazil is a high burden tuberculosis country and has been severely hit by the SARS-CoV-2 pandemic, reporting over 700,000 deaths due to COVID-19.[4] In 2021, the country registered 74,385 cases and 5072 deaths due to tuberculosis.[5] This disease disproportionately affects individuals deprived of liberty, Indigenous people, Pardo and Black people, people experiencing homelessness, and people living with HIV and other comorbidities. Brazil is the largest and most unequal country in Latin America,[6] with significant regional differences in income distribution. Tuberculosis follows this regional pattern with certain states and regions presenting worse epidemiological indicators than others.[5] While the highest tuberculosis incidences are found in the states of Amazonas and Rio de Janeiro, São Paulo, the most populous state in the country, concentrates the highest absolute number of cases.[5]

Previous studies about the impact of the SARS-CoV-2 pandemic on tuberculosis control in Brazil examined the number of tuberculosis notifications at national or regional levels or within prison populations, with many evaluating only the first year of the pandemic.[7–16] Other studies aimed to evaluate patients' and healthcare workers' perceptions on barriers to tuberculosis treatment during the pandemic.[17,18] Overall, there was little information on patient-associated variables. It is unknown if different populational groups were more affected than others from the lack of access to tuberculosis diagnostics, care, and treatment. Understanding the degree at which each one of these subpopulations were affected is key to design public policies for recovery. Therefore, our objectives were to assess the effects of the SARS-CoV-2 pandemic on tuberculosis notifications and identify factors contributing to the decline in notifications and deaths during the pandemic period of 2020 and 2021 in the state of São Paulo.

Methods

Study setting

This study was carried out with data from the state of São Paulo, Brazil, the most populous state in the country, with a population of 46,363,573 million habitants.[19] Its capital, São Paulo, is the 5th most populous city in the world with 12,396,372 people.[19] When adding its metropolitan region of 39 cities, the population rises to 22,048,504 inhabitants. The countryside of the state has 22,417,518 inhabitants (Fig. 1).

Study design and database

This is a retrospective cross-sectional study using data from January 1st, 2016 to December 31st, 2021 obtained through the TBWeb, the tuberculosis notification system of the state of São Paulo. Notification of all cases in

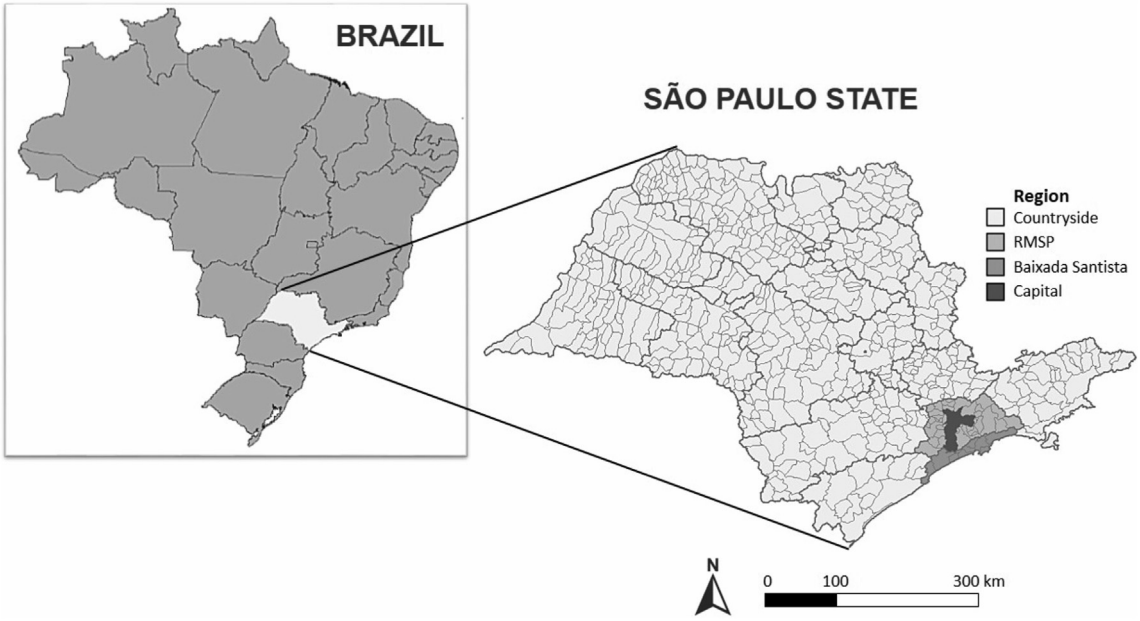

Fig. 1: Study setting. For this study, the state of São Paulo, Brazil was separated into four regions: capital (which is also named São Paulo), metropolitan region of the state capital (RMSP, composed of 39 cities), Baixada Santista, and the countryside.

this system by healthcare workers is mandatory to enable access to tuberculosis medication.

The TBWeb data were made available to the authors of this study in October 2022 by the State Center for Epidemiological Surveillance "Prof. Alexandre Vranjac" without personal identification of patients. This study was approved by the Human Research Ethics Committee of the Institute of Biomedical Sciences, University of São Paulo (Plataforma Brasil, CAAE: 58878322.1.0000.5467, IRB assessment: 5.503.787).

Variables

The main dependent variable used in this study is the total number of tuberculosis cases (new, relapse or re-treatments) reported in each year from 2016 to 2021. The following independent variables were considered: (i) sociodemographic variables: sex (male or female); age group (0–19, 20–49, 50–69, ≥70 years old); ethnicity/race (white, Black, Pardo, East Asian descendants, Indigenous, ignored); schooling (zero, 1–7, 8–14, ≥15 years); region (state capital, metropolitan region of the state capital, Baixada Santista, countryside, population deprived of liberty); type of professional occupation (unemployed, healthcare workers, prison system workers, housewives, people deprived of liberty, retired, or other); population type according to address (people with fixed residency, people deprived of liberty, and people experiencing homelessness); (ii) comorbidities (HIV, mental illness, diabetes, alcoholism, drug addiction, other immunological disease, smoking, no associated comorbidity); (iii) diagnostic tests and treatment: bacilloscopy (positive, negative, in progress, not performed, no information); sputum culture (positive, negative, in progress, not performed, no information); X-ray (suspected tuberculosis, normal, other pathology, suspected tuberculosis with cavity, not performed, no information); HIV test (positive, negative, in progress, not performed, no information); treatment scheme (rifampicin + isoniazid + pyrazinamide, rifampicin + isoniazid + pyrazinamide + ethambutol, other, scheme for multi-drug resistant tuberculosis); type of treatment (directly observed therapy, self-administered, no information); (iv) case type and origin: case type at the time of notification (new case, relapse, re-treatment after abandonment, re-treatment after antibiotic resistance or failure, re-treatment after change in treatment scheme due to adverse events); clinical presentation (extrapulmonary tuberculosis, pulmonary tuberculosis); diagnostic origin (active search at institutions, active search in the community, outpatient demand, contact tracing, urgency/emergency, during hospitalization, post-mortem (autopsy), no information); and (v) outcome (cure, abandonment, death from tuberculosis, death from another cause, change of treatment scheme due to antibiotic resistance/failure, change of treatment scheme due to adverse events, primary abandonment). Descriptions and other details about the variables are shown in Additional Methods in Supplementary Material.

Statistical analyses

Every case notified from 2016 to 2021 was eligible to be included in the study, except duplications (only one notification per patient was kept) (n = 83), those from

individuals presenting a fixed address outside of the state of São Paulo (n = 2), individuals whose diagnosis changed after case notification (i.e., not true tuberculosis cases) (n = 4262), and individuals who changed address to another state or country during the treatment period (n = 1035). Data were analyzed in STATA®13 or R software v. 4.1.1.

Interrupted time series analysis (ITSA) and tuberculosis incidence

An ITSA was performed using tuberculosis notifications on a quarterly basis (every three months) from 2016 to 2021 to estimate the effect of the SARS-CoV-2 pandemic on the number of tuberculosis notifications using R software v.4.1.1. Linear regression and polynomial regressions of different degrees were compared based on R squared, Akaike's Information Criterion (AIC), and Bayesian Information Criterion (BIC) to identify the best model. Based on the tested parameters, a 4th-degree polynomial regression was chosen to model the numbers of tuberculosis cases as the response variable (y) while time (months) was used as the independent variable (x). Intervention and intercept coefficients, F-statistic and their corresponding P-values were calculated. Autocorrelation was tested using Durbin–Watson test, finding no autocorrelation in the residuals (P-value = 0.04). Heteroscedasticity was tested using White test and was absent (P-value = 0.83).

Next, we modelled the trend of notified tuberculosis cases according to the 2016–2019 data by employing a smoothing technique using kernel-weighted polynomials with the Epanechnikov probability density function in a 4th-degree polynomial regression in STATA®13. The input data for this regression consisted of the quarterly number of tuberculosis notifications, weighted based on the frequency observed during the pre-pandemic period (2016–2019) with a 95% confidence interval, as to adjust the trend according to the situation before the COVID-19 pandemic. Based on the adjusted polynomial regression model, expected cases were calculated for each quarter, reflecting the estimated trend of total cases over time.

The annual incidence of tuberculosis per 100,000 habitants was calculated using projection values of the state population in the years 2016–2021 calculated by the Brazilian Institute of Geography and Statistics (SIDRA-IBGE).[20]

Descriptive statistics of independent variables

Data files were grouped into a single database and compiled in STATA®13. The total number of cases, per year (2016–2021), in each category of the independent variables described above was calculated in absolute numbers and percentage. Percentage changes between the last pre-pandemic year (2019) compared to the pandemic years 2020 and 2021 were calculated for each category.

The pandemic years of 2020 and 2021 were compared to 2019 only, and not to the period of 2016–2019, because a steadily, yearly increase in the number of tuberculosis notifications was observed from 2016 to 2019 (see results). This is not a trend specific of the state of São Paulo. The number of tuberculosis notifications in Brazil have been rising since 2016, following a deep political and economic crisis that started in 2014.[7,21] To include all years of 2016–2019 in the comparison analyses would introduce bias, underestimating the impact of the SARS-CoV-2 pandemic on the control of tuberculosis in the state of São Paulo. For this reason, comparisons described next were also made against 2019 only.

Multiple logistic regression for case notification in pandemic periods

Initially, being notified in 2019 (pre-pandemic period) was compared to being notified in 2020 or 2021 (pandemic periods), separately, using Pearson's Chi Square test. The variable sex and variables presenting a P-value $\leq$0.1 in at least one year (2020 and/or 2021) were then included in a multivariable analysis for each comparison (2019 versus 2020 and 2019 versus 2021) using a multiple logistic regression model. Variables associated with (iii) diagnostic tests and treatment, (v) outcome, and those with more than 10% of missing data were not included in the logistic regression analysis (i.e., their corresponding columns were excluded; schooling had 10.4–11.2% of missing data and type of professional occupation had 12.5–14.6% of missing data). Collinearity was checked using variation inflation factor (VIF), in which a value > 10 defined a collinear variable. The variables "region" and "population type according to address" presented collinearity because of the categories of people deprived of liberty; "region" was then excluded from the analysis. As per the software default, rows with missing data were skipped during the statistical analysis. Odds Ratio (OR), the Confidence Interval (CI) for OR and the P-value, with a confidence level (α) of 5% were calculated. Model fit was assessed using the Hosmer–Lemeshow test, AIC, and BIC.

Risk factors for death from tuberculosis

For this analysis, the dependent variable was "outcome", but only the patients within the categories "death from tuberculosis" and "cure" were compared. Two separate multivariable analyses using Firth's logistic regression were performed to identify risk factors associated with death from tuberculosis in pre-pandemic year (2019) and pandemic years (2020/2021). Variables associated with (iv) diagnostic origin, (v) outcome, and those with more than 10% of missing data (i.e., schooling and type of professional occupation) were not included (i.e., their corresponding columns were excluded). The variable treatment scheme was also not included because most individuals diagnosed post-mortem are classified as

"other treatment scheme"; this variable does not have the option of "no information". Diagnostic origin was not included because one of the categories is post-mortem diagnostics (autopsy). The variables "region" and "population type according to address" presented collinearity because of the categories of people deprived of liberty; "region" was then excluded from the analysis. As per the software default, rows with missing data were skipped during the statistical analysis. OR, CI for OR and the P-value, with a confidence level (α) of 5% were calculated. Model fit was assessed using the likelihood ratio test, AIC, and BIC.

Role of funding source

This study was funded by the Brazilian National Council for Scientific and Technological Development (CNPq), the Brazilian Coordination for the Improvement of Higher Education Personnel (CAPES), and by São Paulo Research Foundation (FAPESP). The funders had no role in study design, data collection, analysis, interpretation, writing, or decision to submit the manuscript.

Results

Descriptive statistics and tuberculosis cases trend

From 2016 to 2021, 126,649 tuberculosis cases (study-eligible) were notified in the state of São Paulo, varying from 19,762 to 22,313 cases per year, with the highest and lowest number of cases notified in 2018 and 2020, respectively (Table 1). Total tuberculosis cases were increasing from 2016 to 2019, when a significant decline occurred associated with the detection of the first case of SARS-CoV-2 in Brazil (February 26th, 2020) and the beginning of lockdown measures (March 2020) (Fig. 2 and Table 1). The ITSA indicates that the number of tuberculosis notifications was significantly lower in the pandemic period compared to the pre-pandemic period (intervention coefficient: –610,116.5, P-value = 0.03) (Supplementary Tables S1 and S2). Additionally, observed quarterly numbers of tuberculosis notifications during the pandemic period (2020–2021) did not follow the expected number of cases according to the pre-established trend of 2016–2019 (Supplementary Fig. S1 and Table S3). Overall, the numbers of observed cases were consistently lower in all analyzed quarters of the pandemic period (2020–2021) compared to the expected number of cases for that period, with percentual differences varying from –0.52% to –15.82% (Supplementary Table S3). However, there was an important recovery in notifications in the last two quarters of 2021 (Supplementary Fig. S1), being only –0.92% and –0.52% below the expected number of cases for that period (Supplementary Table S3).

Similarly, the tuberculosis incidence in the state of São Paulo declined –11.5% in 2020 and –11.0% in 2021 compared to 2019 (Table 2). The incidence of tuberculosis in the state of São Paulo has shown significant regional differences over years.[22] Baixada Santista showed the highest annual tuberculosis incidence since 2016, being 4–5 times higher than the countryside (Table 2). Higher percentage declines in the tuberculosis incidence of the metropolitan region of the state capital and Baixada Santista were observed (Table 2). In 2021, there was only minimal increase in tuberculosis incidence in the capital compared to 2020. However, the incidence remained unchanged in the metropolitan region of the state capital and in the countryside, and it decreased in Baixada Santista compared to 2020 (Table 2).

Year 2020 compared to 2019—descriptive statistics

The percentage decline in the total number of tuberculosis notifications in 2020 compared to 2019 was –10.2%. Nineteen categories from 12 independent variables showed percentage declines in notifications that were 1.5 times or higher (≥–15%) than the –10.2% (Table 1), suggesting that the negative effect of the pandemic was unequal across different population strata. The 12 variables and their categories were: age group (0-19 years-old, –16.3%), ethnicity/race (East Asian descendants, –15.9%), schooling (zero years, –32.1%), type of professional occupation (housewives, –16.3%; retired, –17.8%), comorbidities (HIV positive, –16.4%; no associated comorbidity, –15.1%), diagnostic tests (negative bacilloscopy, –15.9%; negative sputum culture, –17.5%; sputum culture in progress, –52.9%; normal x-ray, –17.4%; other pathology in x-ray, –21.3%; HIV positive test, –16.0%; HIV test not performed, –23.1%), treatment scheme (rifampicin + isoniazid + pyrazinamide, –31.3%), and diagnostic origin (diagnosed post-mortem, –24.7%; diagnosed through contact tracing, –25.0%; diagnosed at urgency/emergency facilities, –18.9%; no information, –26.9%). The large percentage declines described above for bacilloscopy, sputum culture, x-ray, and HIV test are likely explained by an increase in the number of cases classified with "no information" for these diagnostic tests, which ranged from +1.7% to +26.7% (Table 1). Noteworthy, notifications with directly observed therapy declined –14.3%.

Despite the overall decline in tuberculosis notifications, certain categories appeared with a higher number of cases in 2020 compared to 2019. There was an increase of 1.5% in tuberculosis notifications among healthcare workers (from 273 in 2019 to 277 in 2020), 0.4% increase among individuals with diabetes (from 1501 to 1507), 6.7% increase among patients with other immunological diseases (i.e., not HIV) (from 253 to 270), and 4.6% increase in "re-treatment after change in treatment scheme due to adverse events" (from 151 to 158). Most importantly, there was a 5.0% increase in deaths from tuberculosis (from 753 cases in 2019 to 791 cases in 2020), a 2.0% increase in deaths due to other causes (from 885 to 903 cases), a 9.2% increase in

Variable	2016		2017		2018		2019		2020		2021		Total		PC%	PC%
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	2020	2021
Total cases notified in the state of São Paulo	20,323	100	22,015	100	22,313	100	22,011	100	19,762	100	20,225	100	126,649	100	−10.2%	−8.1%
Sociodemographic variables																
Sex																
Female	5485	26.99	5717	25.97	6046	27.10	6131	27.85	5524	27.95	5714	28.25	34,617	27.33	−9.9%	−6.8%
Male	14,838	73.01	16,298	74.03	16,267	72.90	15,880	72.15	14,238	72.05	14,511	71.75	92,032	72.67	−10.3%	−8.6%
Total	20,323	100	22,015	100	22,313	100	22,011	100	19,762	100	20,225	100	126,649	100	−10.2%	−8.1%
P-value															0.82	0.36
Age group (years-old)																
0–19	1569	7.73	1744	7.93	1705	7.65	1679	7.64	1406	7.12	1397	6.91	9500	7.51	**−16.3%**	**−16.8%**
20–49	13,831	68.15	15,028	68.37	15,135	67.89	14,657	66.65	13,338	67.56	13,484	66.73	85,473	67.56	−9.0%	−8.0%
50–69	4058	20.00	4335	19.72	4547	20.40	4694	21.35	4151	21.03	4426	21.90	26,211	20.72	−11.6%	−5.7%
≥70	836	4.12	873	3.97	907	4.07	960	4.37	847	4.29	900	4.45	5323	4.21	−11.8%	−6.3%
Total	20,294	100	21,980	100	22,294	100	21,990	100	19,742	100	20,207	100	126,507	100	−10.2%	−8.1%
P-value															0.13	**0.03**
Ethnicity/race																
White	8413	44.68	9042	44.02	8999	43.30	8584	41.95	7463	40.45	7440	39.69	49,941	42.39	−13.1%	**−13.3%**
Black	2181	11.58	2355	11.46	2466	11.87	2449	11.97	2333	12.65	2450	13.07	14,234	12.08	−4.7%	0.0%
Pardo	7259	38.55	8060	39.24	8278	39.83	8226	40.20	7590	41.14	7807	41.65	47,220	40.08	−7.7%	−5.1%
East Asian descendants	138	0.73	164	0.80	162	0.78	164	0.80	138	0.75	164	0.87	930	0.79	**−15.9%**	0.0%
Indigenous	69	0.37	51	0.25	49	0.24	30	0.15	30	0.16	26	0.14	255	0.22	0.0%	**−13.3%**
Ignored	769	4.08	869	4.23	829	3.99	1008	4.93	895	4.85	856	4.57	5226	4.44	−11.2%	**−15.1%**
Total	18,829	100	20,541	100	20,783	100	20,461	100	18,449	100	18,743	100	117,806	100	−9.8%	−8.4%
P-value															**0.04**	**<0.001**
Schooling (years)																
Zero	525	2.88	544	2.74	530	2.62	557	2.83	378	2.15	385	2.17	2919	2.58	**−32.1%**	**−30.9%**
1–7	7152	39.29	7687	38.68	7713	38.16	6972	35.38	6119	34.83	6105	34.38	41,748	36.84	−12.2%	**−12.4%**
8–14	7294	40.07	7918	39.84	7995	39.56	7939	40.29	7226	41.13	7325	41.25	45,697	40.33	−9.0%	−7.7%
≥15	528	2.90	577	2.90	652	3.23	641	3.25	555	3.16	563	3.17	3516	3.10	−13.4%	**−12.2%**
Ignored	2706	14.86	3148	15.84	3320	16.43	3595	18.25	3291	18.73	3381	19.04	19,441	17.16	−8.5%	−6.0%
Total	18,205	100	19,874	100	20,210	100	19,704	100	17,569	100	17,759	100	113,321	100	−10.8%	−9.9%
P-value															**<0.001**	**<0.001**
Region																
Capital	6704	32.99	7180	32.61	7562	33.89	7659	34.80	7018	35.51	7245	35.82	43,368	34.24	−8.4%	−5.4%
Metropolitan region of the state capital	3417	16.81	3618	16.43	3815	17.10	3859	17.53	3450	17.46	3600	17.80	21,759	17.18	−10.6%	−6.7%
Baixada Santista	1887	9.29	1885	8.56	2081	9.33	2111	9.59	1912	9.68	1962	9.70	11,838	9.35	−9.4%	−7.1%
Countryside	5199	25.58	5538	25.16	5747	25.76	5724	26.01	5059	25.60	5412	26.76	32,679	25.80	−11.6%	−5.5%
People deprived of liberty	3116	15.33	3794	17.23	3108	13.93	2658	12.08	2323	11.75	2006	9.92	17,005	13.43	−12.6%	**−24.5%**

(Table 1 continues on next page)

Variable	2016		2017		2018		2019		2020		2021		Total		PC%	PC%
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	2020	2021
(Continued from previous page)																
Total	20,323	100	22,015	100	22,313	100	22,011	100	19,762	100	20,225	100	126,649	100	−10.2%	−8.1%
P-value															0.53	**<0.001**
Type of professional occupation																
Unemployed	3024	16.70	3330	17.06	3728	18.69	3722	19.28	3357	19.94	3290	19.74	20,451	18.53	−9.8%	−11.6%
Healthcare workers	223	1.23	255	1.31	252	1.26	273	1.41	277	1.65	243	1.46	1523	1.38	**1.5%**	−11.0%
Prison system workers	35	0.19	34	0.17	33	0.17	25	0.13	23	0.14	42	0.25	192	0.17	−8.0%	**68.0%**
Housewives	1190	6.57	1198	6.14	1279	6.41	1224	6.34	1025	6.09	1021	6.12	6937	6.28	**−16.3%**	**−16.6%**
People deprived of liberty	3035	16.76	3725	19.09	3123	15.66	2646	13.71	2300	13.66	2111	12.66	16,940	15.35	−13.1%	**−20.2%**
Retired	1149	6.34	1174	6.02	1240	6.22	1224	6.34	1006	5.98	1024	6.14	6817	6.18	**−17.8%**	**−16.3%**
Other occupation	9454	52.20	9800	50.22	10,288	51.59	10,190	52.79	8844	52.54	8939	53.62	57,515	52.11	−13.2%	**−12.3%**
Total	18,110	100	19,516	100	19,943	100	19,304	100	16,832	100	16,670	100	110,375	100	−12.8%	**−13.6%**
P-value															0.28	**<0.001**
Population type according to address																
Fixed residency	16,308	80.24	17,182	78.05	18,128	81.24	18,247	82.90	16,386	82.92	17,184	84.96	103,435	81.67	−10.2%	−5.8%
People deprived of liberty	3120	15.35	3794	17.23	3110	13.94	2669	12.13	2324	11.76	2011	9.94	17,028	13.45	−12.9%	**−24.7%**
People experiencing homelessness	895	4.40	1039	4.72	1075	4.82	1095	4.97	1052	5.32	1030	5.09	6186	4.88	−3.9%	−5.9%
Total	20,323	100	22,015	100	22,313	100	22,011	100	19,762	100	20,225	100	126,649	100	−10.2%	−8.1%
P-value															0.16	**<0.001**
Comorbidities																
HIV																
No	18,510	91.08	20,102	91.31	20,390	91.38	20,140	91.50	18,198	92.09	18,648	92.20	115,988	91.58	−9.6%	−7.4%
Yes	1813	8.92	1913	8.69	1923	8.62	1871	8.50	1564	7.91	1577	7.80	10,661	8.42	**−16.4%**	**−15.7%**
P-value															0.03	0.01
Mental illness																
No	20,017	98.49	21,694	98.54	21,955	98.40	21,693	98.56	19,451	98.43	19,918	98.48	124,728	98.48	−10.3%	−8.2%
Yes	306	1.51	321	1.46	358	1.60	318	1.44	311	1.57	307	1.52	1921	1.52	−2.2%	−3.5%
P-value															0.28	0.53
Diabetes																
No	19,095	93.96	20,673	93.90	20,843	93.41	20,510	93.18	18,255	92.37	18,642	92.17	118,018	93.19	−11.0%	−9.1%
Yes	1228	6.04	1342	6.10	1470	6.59	1501	6.82	1507	7.63	1583	7.83	8631	6.81	**0.4%**	**5.5%**
P-value															**<0.001**	**<0.001**
Alcoholism																
No	16,620	81.78	17,936	81.47	17,900	80.22	17,596	79.94	15,808	79.99	16,088	79.55	101,948	80.50	−10.2%	−8.6%
Yes	3703	18.22	4079	18.53	4413	19.78	4415	20.06	3954	20.01	4137	20.45	24,701	19.50	−10.4%	−6.3%
P-value															0.90	0.31

(Table 1 continues on next page)

Variable	2016		2017		2018		2019		2020		2021		Total		PC%	PC%
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	2020	2021
(Continued from previous page)																
Drug addiction																
No	16,842	82.87	17,813	80.91	17,696	79.31	17,576	79.85	15,935	80.63	16,236	80.28	102,098	80.61	−9.3%	−7.6%
Yes	3481	17.13	4202	19.09	4617	20.69	4435	20.15	3827	19.37	3989	19.72	24,551	19.39	−13.7%	−10.1%
P-value															**0.05**	0.27
Other immunological disease																
No	20,068	98.75	21,750	98.80	22,036	98.76	21,758	98.85	19,492	98.63	19,996	98.87	125,100	98.78	−10.4%	−8.1%
Yes	255	1.25	265	1.20	277	1.24	253	1.15	270	1.37	229	1.13	1549	1.22	**6.7%**	−9.5%
P-value															**0.05**	0.87
Smoking																
No	15,491	76.22	16,362	74.32	16,221	72.70	16,155	73.40	14,481	73.28	14,715	72.76	93,425	73.77	−10.4%	−8.9%
Yes	4832	23.78	5653	25.68	6092	27.30	5856	26.60	5281	26.72	5510	27.24	33,224	26.23	−9.8%	−5.9%
P-value															0.78	0.14
No associated comorbidity																
No	13,659	67.21	14,867	67.53	15,471	69.34	15,451	70.20	14,191	71.81	14,393	71.16	88,032	69.51	−8.2%	−6.8%
Yes	6664	32.79	7148	32.47	6842	30.66	6560	29.80	5571	28.19	5832	28.84	38,617	30.49	**−15.1%**	−11.1%
Total	20,323	100	22,015	100	22,313	100	22,011	100	19,762	100	20,225	100	126,649	100	−10.2%	−8.1%
P-value															**<0.001**	**0.03**
Diagnostic tests and treatment																
Bacilloscopy																
Positive	10,641	52.41	10,712	48.66	10,234	45.87	10,026	45.55	8850	44.78	9220	45.59	59,683	47.13	−11.7%	−8.0%
Negative	4753	23.41	4794	21.78	4666	20.91	4489	20.39	3775	19.10	3673	18.16	26,150	20.65	**−15.9%**	**−18.2%**
In progress	41	0.20	32	0.15	96	0.43	66	0.30	60	0.30	71	0.35	366	0.29	−9.1%	**7.6%**
Not performed	4726	23.28	6358	28.88	7171	32.14	7269	33.02	6873	34.78	7004	34.63	39,401	31.12	−5.4%	−3.6%
No information	143	0.70	119	0.54	146	0.65	161	0.73	204	1.03	256	1.27	1029	0.81	**26.7%**	**59.0%**
Total	20,304	100	22,015	100	22,313	100	22,011	100	19,762	100	20,224	100	126,629	100	−10.2%	−8.1%
P-value															**<0.001**	**<0.001**
Sputum culture																
Positive	7019	34.94	8468	38.46	7779	34.86	7666	34.83	6995	35.40	6208	30.69	44,135	34.91	−8.8%	**−19.0%**
Negative	2514	12.51	2790	12.67	2732	12.24	2854	12.97	2354	11.91	2306	11.40	15,550	12.30	**−17.5%**	**−19.2%**
In progress	199	0.99	114	0.52	215	0.96	223	1.01	105	0.53	252	1.25	1108	0.88	**−52.9%**	**13.0%**
Not performed	10,023	49.89	10,270	46.65	11,135	49.90	10,836	49.23	9822	49.70	10,803	53.41	62,889	49.75	−9.4%	−0.3%
No information	336	1.67	373	1.69	452	2.03	432	1.96	486	2.46	656	3.24	2735	2.16	**12.5%**	**51.9%**
Total	20,091	100	22,015	100	22,313	100.00	22,011	100	19,762	100	20,225	100	126,417	100	−10.2%	−8.1%
P-value															**<0.001**	**<0.001**

(Table 1 continues on next page)

Variable	2016		2017		2018		2019		2020		2021		Total		PC%	PC%
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	2020	2021
(Continued from previous page)																
X-ray																
Suspected TB	10,263	53.12	10,578	50.76	11,113	52.62	11,108	52.84	9850	51.89	9239	48.11	62,151	51.58	−11.3%	**−16.8%**
Normal	1144	5.92	1174	5.63	1212	5.74	1244	5.92	1027	5.41	994	5.18	6795	5.64	**−17.4%**	**−20.1%**
Other pathology	246	1.27	265	1.27	278	1.32	272	1.29	214	1.13	185	0.96	1460	1.21	**−21.3%**	**−32.0%**
Suspected TB with cavity	2647	13.70	2936	14.09	3017	14.28	2948	14.02	2508	13.21	2618	13.63	16,674	13.84	−14.9%	−11.2%
Not performed	4422	22.89	5240	25.14	4865	23.03	4656	22.15	4478	23.59	5305	27.62	28,966	24.04	−3.8%	**13.9%**
No information	600	3.11	648	3.11	636	3.01	793	3.77	906	4.77	863	4.49	4446	3.69	**14.2%**	**8.8%**
Total	19,322	100	20,841	100	21,121	100	21,021	100	18,983	100	19,204	100	120,492	100	−9.7%	−8.6%
P-value															**<0.001**	**<0.001**
HIV test																
Positive	1953	9.73	2022	9.29	2043	9.32	2009	9.29	1687	8.66	1685	8.48	11,399	9.14	**−16.0%**	**−16.1%**
Negative	16,403	81.76	18,142	83.31	18,116	82.62	17,825	82.41	16,334	83.88	16,473	82.92	103,293	82.81	−8.4%	−7.6%
In progress	95	0.47	54	0.25	94	0.43	83	0.38	77	0.40	122	0.61	525	0.42	−7.2%	**47.0%**
Not performed	1492	7.44	1462	6.71	1494	6.81	1483	6.86	1140	5.85	1307	6.58	8378	6.72	**−23.1%**	−11.9%
No information	119	0.59	97	0.45	180	0.82	230	1.06	234	1.20	278	1.40	1138	0.91	**1.7%**	**20.9%**
Total	20,062	100	21,777	100	21,927	100	21,630	100	19,472	100	19,865	100	124,733	100	−10.0%	−8.2%
P-value															**<0.001**	**<0.001**
Treatment scheme																
Rifampicin + isoniazid + pyrazinamide	294	1.45	357	1.62	390	1.75	393	1.79	270	1.37	262	1.30	1966	1.55	**−31.3%**	**−33.3%**
Rifampicin + isoniazid + pyrazinamide + ethambutol	19,042	93.70	20,566	93.42	20,915	93.73	20,520	93.23	18,486	93.54	18,883	93.36	118,412	93.50	−9.9%	−8.0%
Other	987	4.86	1092	4.96	1008	4.52	1097	4.98	1005	5.09	1080	5.34	6269	4.95	−8.4%	−1.5%
Scheme for multi-drug resistant tuberculosis[a]	0	0.00	0	0.00	0	0.00	1	0.00	1	0.01	0	0.00	2	0.00	0.0%	**−100%**
Total	20,323	100	22,015	100	22,313	100	22,011	100	19,762	100	20,225	100	126,649	100	−10.2%	−8.1%
P-value															**0.01**	**<0.001**
Type of treatment																
Directly observed therapy	15,078	80.92	16,952	80.72	16,696	79.24	15,973	77.02	13,693	75.99	13,675	79.21	92,067	79.21	−14.3%	**−14.4%**
Self-administered	3479	18.67	3912	18.40	3806	19.33	3897	21.48	3819	22.17	3990	19.70	22,903	19.70	−2.0%	**2.4%**
No information	111	0.41	85	0.88	182	1.43	289	1.50	267	1.84	331	1.09	1265	1.09	−7.6%	**14.5%**
Total	18,668	100	20,949	100	20,684	100	20,159	100	17,779	100	17,996	100	116,235	100	−11.8%	−10.7%
P-value															**<0.001**	**<0.001**
Case type and origin																
Case type at the time of notification																
New case	16,780	82.57	18,183	82.59	18,289	81.97	17,906	81.35	15,954	80.73	16,158	79.89	103,270	81.54	−10.9%	−9.8%
Relapse	1943	9.56	2245	10.20	2239	10.03	2206	10.02	1983	10.03	2002	9.90	12,618	9.96	−10.1%	−9.2%
Re-treatment after abandonment	1439	7.08	1366	6.20	1521	6.82	1585	7.20	1517	7.68	1663	8.22	9091	7.18	−4.3%	**4.9%**
Re-treatment after antibiotic resistance or failure	128	0.63	162	0.74	152	0.68	163	0.74	150	0.76	163	0.81	918	0.72	−8.0%	0.0%

(Table 1 continues on next page)

Variable	2016		2017		2018		2019		2020		2021		Total		PC%	PC%
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	2020	2021
(Continued from previous page)																
Re-treatment after adverse events[b]	33	0.16	59	0.27	112	0.50	151	0.69	158	0.80	239	1.18	752	0.59	**4.6%**	**58.3%**
Total	20,323	100	22,015	100	22,313	100	22,011	100	19,762	100	20,225	100	126,649	100	−10.2%	−8.1%
P-value															0.24	**<0.001**
Clinical presentation																
Extrapulmonary tuberculosis	2877	14.16	2891	13.13	3137	14.06	3256	14.79	2804	14.19	2798	13.83	17,763	14.03	−13.9%	**−14.1%**
Pulmonary tuberculosis	17,446	85.84	19,124	86.87	19,176	85.94	18,755	85.21	16,958	85.81	17,427	86.17	108,886	85.97	−9.6%	−7.1%
Total	20,323	100	22,015	100	22,313	100	22,011	100	19,762	100	20,225	100	126,649	100	−10.2%	−8.1%
P-value															0.08	**0.01**
Diagnostic origin																
Active search at institutions	1111	5.59	1387	6.48	1252	5.75	1103	5.15	1031	5.36	979	4.98	6863	5.56	−6.5%	−11.2%
Active search in the community	432	2.17	470	2.19	526	2.42	499	2.33	455	2.36	409	2.08	2791	2.26	−8.8%	**−18.0%**
Outpatient demand	9974	50.20	10,761	50.25	10,735	49.34	10,909	50.94	10,119	52.56	10,810	54.95	63,308	51.31	−7.2%	−0.9%
Post-mortem (autopsy)	232	1.17	264	1.23	234	1.08	239	1.12	180	0.93	212	1.08	1361	1.10	**−24.7%**	−11.3%
Contact tracing	544	2.74	703	3.28	689	3.17	629	2.94	472	2.45	391	1.99	3428	2.78	**−25.0%**	**−37.8%**
Urgency/Emergency	4190	21.09	4202	19.62	4380	20.13	4482	20.93	3635	18.88	3691	18.76	24,580	19.92	**−18.9%**	**−17.6%**
During hospitalization	3302	16.62	3561	16.63	3864	17.76	3476	16.23	3304	17.16	3090	15.71	20,597	16.69	−4.9%	−11.1%
No information	84	0.42	68	0.32	79	0.36	78	0.36	57	0.30	91	0.46	457	0.37	**−26.9%**	**16.7%**
Total	19,869	100	21,416	100	21,759	100	21,415	100	19,253	100	19,673	100	123,385	100	−10.1%	−8.1%
P-value															**<0.001**	**<0.001**
Outcome																
Cure	16,070	79.41	17,152	78.32	17,261	78.11	16,606	76.38	14,319	73.64	13,415	70.96	94,823	76.27	−13.8%	**−19.2%**
Abandonment	2327	11.50	2686	12.26	2796	12.65	2985	13.73	2918	15.01	3228	17.07	16,940	13.63	−2.2%	**8.1%**
Death from tuberculosis	676	3.34	759	3.47	760	3.44	753	3.46	791	4.07	849	4.49	4588	3.69	**5.0%**	**12.7%**
Death from another cause	871	4.30	907	4.14	859	3.89	885	4.07	903	4.64	884	4.68	5309	4.27	**2.0%**	−0.1%
Change in treatment due to resistance	124	0.61	180	0.82	156	0.71	171	0.79	147	0.76	164	0.87	942	0.76	−14.0%	−4.1%
Change in treatment due to adverse events	42	0.21	81	0.37	131	0.59	184	0.85	201	1.03	256	1.35	895	0.72	**9.2%**	**39.1%**
Primary abandonment	127	0.63	136	0.62	135	0.61	158	0.73	165	0.85	110	0.58	831	0.67	**4.4%**	**−30.4%**
Total	20,237	100	21,901	100	22,098	100	21,742	100	19,444	100	18,906	100	124,328	100	−10.6%	**−13.0%**
P-value															**<0.001**	**<0.001**

P-values ≤0.05 are in bold. PC% 2020 ≥−15%, PC% 2021 ≥−12% and PC% with positive values are in bold. P-values were generated using Pearson's Chi Square test, comparing 2019 to 2020 and 2019 to 2021. [a]Data on multi-drug resistance is likely underestimated because data from patients with drug-resistant tuberculosis are managed in another system called SITE-TB (not analyzed herein), with many being classified in the category "other" or never updated. [b]Re-treatment after change in treatment scheme due to adverse events.

Table 1: **Descriptive statistics of notified tuberculosis (TB) cases in the state of São Paulo from 2016 to 2021 and percentage change (PC%) in the number of TB cases in 2020 (first pandemic year) compared to 2019 (pre-pandemic year) and 2021 (second pandemic year) compared to 2019 (pre-pandemic year).**

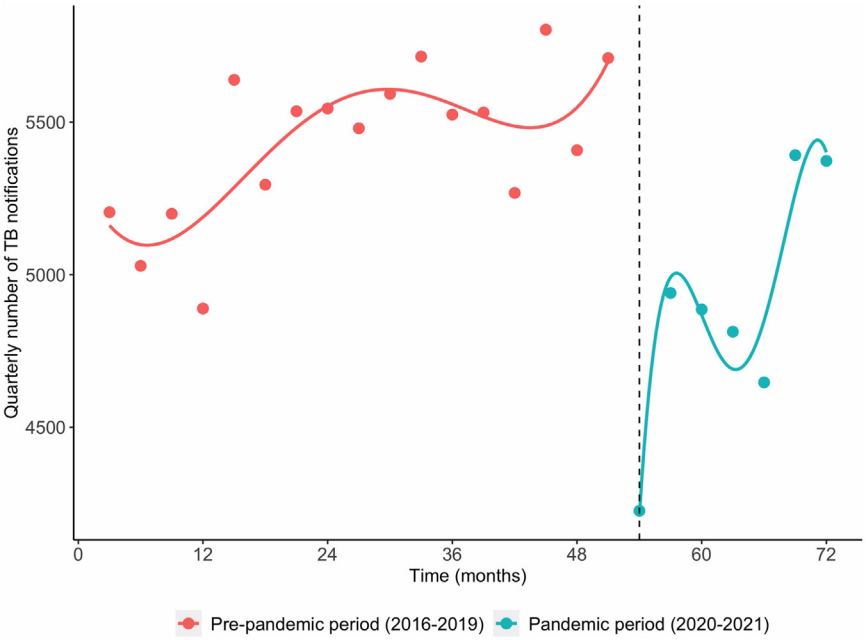

Fig. 2: Tuberculosis (TB) cases notified quarterly (i.e., every three months) in the state of São Paulo, Brazil from 2016 to 2021. Interrupted time series analysis using 4th-degree smoothed polynomial regression of TB cases notified per month in TBWeb from January 2016 to December 2021. The first case of COVID-19 was detected in São Paulo, Brazil on February 26th, 2020. Lockdown periods ensued thereafter throughout different regions in the state and country in a heterogeneous manner. Dashed line represents the beginning of lockdown periods. Analysis and figures were performed in R software v. 4.1.1 with ggplot and lm (poly).

"change in treatment due to adverse events" (from 184 to 201 cases), and a 4.4% increase in primary abandonment (from 158 to 165 cases). Interestingly, the number of cases with "change in treatment due to adverse events" increased almost 6 times in six years, from 42 cases in 2016 to 256 cases in 2021. In addition, the number of tuberculosis cases among people with diabetes increased from 1228 in 2016 to 1583 in 2021 (Table 1).

Year 2021 compared to 2019—descriptive statistics

The percentage decline in the total number of tuberculosis notifications in 2021 compared to 2019 was –8.1%. Twenty-nine categories of 16 independent variables showed percentage declines that were 1.5 times or higher (≥–12%) than the overall –8.1% (Table 1). The number of categories/variables with changes is higher than the one observed in 2020 (n = 19 categories and 12 variables), suggesting that the inequality in notification among different populational strata increased in 2021. A total of 13/19 categories with high percentage declines in 2020 remained with high percentage declines in 2021, which include: age group (0-19 years-old, –16.8%), schooling (zero years, –30.9%), type of professional occupation (housewives, –16.6%; retired, –16.3%), comorbidities (HIV positive, –15.7%), diagnostic tests (negative bacilloscopy, –18.2%; negative sputum culture, –19.2%; normal x-ray, –20.1%; other pathology in x-ray, –32.0%; HIV positive test, –16.1%), treatment scheme (rifampicin + isoniazid + pyrazinamide, –33.3%), and diagnostic origin (diagnosed through contact tracing, –37.8%; diagnosed at urgency/emergency facilities, –17.6%). Other categories that emerged in 2021 with high percentage declines include: ethnicity/race (white, –13.3%; Indigenous, –13.3%; ignored, –15.1%); schooling (1–7 years, –12.4%; ≥15 years, –12.2%); region (people deprived of liberty, –24.5%); type of professional occupation (people deprived of liberty, –20.2%; other occupation, –12.3%); population type according to address (people deprived of liberty, –24.7%); diagnostic tests (positive sputum culture, –19.0%; suspected tuberculosis on x-ray, –16.8%); type of treatment (directly observed therapy, –14.4%); clinical presentation (extrapulmonary tuberculosis, –14.1%); diagnostic origin (active search in the community, –18.0%); outcome (cure, –19.2%; primary abandonment, –30.4%). As observed in 2020, the large percentage declines described above for bacilloscopy, sputum culture, x-ray, and HIV test are likely explained by an increase in the number of cases classified with "no information" for these diagnostic tests (Table 1). A main highlight of 2021 was the important decline in notification among people deprived of liberty with a concomitant increase in the number of notifications among workers of the prison system, which

Year	2016		2017		2018		2019		2020		2021		PC% 2020	PC% 2021
	coef	95% CI	coef	95% CI	coef	95% CI	coef	95% CI	coef	95% CI	coef	95% CI		
Capital	45.28	(44.59–45.98)	48.58	(47.88–49.29)	50.83	(50.12–51.54)	50.82	(50.12–51.54)	45.09	(44.41–45.79)	46.35	(45.67–47.05)	−11.3%	−8.8%
RMSP	13.84	(13.46–14.23)	14.42	(14.04–14.81)	15.15	(14.77–15.55)	15.15	(14.76–15.54)	13.30	(12.93–13.67)	13.65	(13.28–14.02)	−12.2%	−9.9%
Baixada Santista	82.51	(80.48–84.59)	82.23	(80.21–84.3)	89.25	(87.21–91.35)	90.49	(88.45–92.58)	82.21	(80.22–84.26)	79.26	(77.29–81.28)	−9.1%	−12.4%
Countryside	20.59	(20.17–21.02)	21.77	(21.34–22.2)	22.04	(21.61–22.47)	21.46	(21.05–21.89)	19.14	(18.73–19.55)	19.90	(19.49–20.31)	−10.8%	−7.3%
State of SP	37.50	(37.15–37.84)	40.32	(39.97–40.67)	40.26	(39.91–40.60)	39.14	(38.79–39.48)	34.63	(34.3–34.97)	34.85	(34.52–35.19)	−11.5%	−11.0%

RMSP, metropolitan region of the state capital; CI, confidence interval; PC%, percentage change (2020 compared to 2019; 2021 compared to 2019).

Table 2: **Incidence of tuberculosis per 100,000 habitants in different regions of the state of São Paulo (SP).**

increased from 25 cases in 2019 to 42 cases in 2021. In 2020, the percentage decline in cases among people deprived of liberty was already above average (−12.9%).

In addition to the 68.0% increase in tuberculosis cases among prison workers, there was a 5.5% increase in cases among people with diabetes (from 1501 in 2019 to 1583 in 2021), a 2.4% increase in self-administered treatment (from 3897 to 3990), a 14.5% increase in "no information" about how the treatment was being administered (from 289 to 331), 4.9% increase in "re-treatment after abandonment" (from 1585 to 1663), 58.3% increase in "re-treatment after change in treatment scheme due to adverse events" (from 151 to 239), and a 16.7% increase in cases with "no information" regarding the diagnostic origin (from 78 to 91). Importantly, deaths due to tuberculosis increased 12.7% (from 753 cases in 2019 to 849 cases in 2021), abandonment increased 8.1% (from 2985 cases in 2019 to 3228 cases in 2021), and "change in treatment due to adverse events" increased 39.1% (from 184 cases in 2019 to 256 cases in 2021) (Table 1).

Factors associated with tuberculosis notifications in 2020 and 2021 compared to 2019

The completeness in data entry for each one of the 25 independent variables analyzed in this study was considered good (Supplementary Table S4). Only "schooling" and "type of professional occupation" showed more than 10% of missing data (Supplementary Table S4).

Two multiple logistic regressions were conducted to identify factors associated with tuberculosis notification in pandemic years. The first analysis compared 2019 (pre-pandemic year) to 2020 (first pandemic year), while the second compared 2019 (pre-pandemic year) to 2021 (second pandemic year) (Table 3). The odds of being notified as a tuberculosis case in 2020 were significantly lower among people deprived of liberty (OR = 0.91), people with HIV (OR = 0.87), drug addiction (OR = 0.89) and those without any comorbidity (OR = 0.90) (Table 3). The odds of being notified as a tuberculosis case in 2020 were also significantly lower among those diagnosed post-mortem (autopsy) (OR = 0.76), through contact tracing (OR = 0.78) and at the urgency/emergency facilities (OR = 0.83) compared to those diagnosed during active search at institutions (e.g. prisons, mental health hospitals, nursing homes and shelters).

The odds of being notified in 2021 as a tuberculosis case were likewise significantly lower among people deprived of liberty (OR = 0.72), people with HIV (OR = 0.89) and drug addiction (OR = 0.94), and those individuals diagnosed during active search in the community (OR = 0.72), through contact tracing (OR = 0.58), at urgency/emergency facilities (OR = 0.75), and during hospitalizations (OR = 0.83), compared to active search at

Variables	2019 versus 2020			2019 versus 2021		
	OR	95% CI	P-value	OR	95% CI	P-value
Sociodemographic variables						
Sex						
Female	1			1		
Male	0.98	0.94–1.03	0.52	1.00	0.95–1.05	0.97
Age group (years old)						
0–19	1			1		
20–49	1.05	0.97–1.14	0.24	1.07	0.99–1.17	0.08
50–69	0.98	0.90–1.07	0.65	1.05	0.96–1.15	0.31
≥70	0.95	0.84–1.08	0.41	1.02	0.90–1.16	0.71
Ethnicity/race						
White	1			1		
Black	1.11	1.04–1.18	**<0.001**	1.18	1.11–1.26	**<0.001**
Pardo	1.07	1.03–1.12	**<0.001**	1.11	1.07–1.17	**<0.001**
East Asian descendants	1.00	0.79–1.26	0.98	1.13	0.90–1.41	0.30
Indigenous	1.12	0.67–1.89	0.67	1.02	0.60–1.73	0.95
Ignored	1.03	0.94–1.14	0.54	1.00	0.90–1.10	0.97
Population type according to address						
Fixed address	1			1		
People deprived of liberty	0.91	0.84–0.97	**0.01**	0.72	0.67–0.78	**<0.001**
People experiencing homelessness	1.06	0.96–1.16	0.23	0.96	0.87–1.05	0.39
Comorbidities						
HIV (yes)	0.87	0.80–0.94	**<0.001**	0.89	0.83–0.97	**<0.001**
Diabetes (yes)	1.09	1.01–1.19	**0.03**	1.14	1.05–1.23	**<0.001**
Drug addiction (yes)	0.89	0.84–0.94	**<0.001**	0.94	0.88–0.99	**0.02**
Other immunological diseases (yes)	1.09	0.91–1.31	0.34	0.92	0.76–1.11	0.40
No associated comorbidity (yes)	0.90	0.85–0.94	**<0.001**	0.96	0.92–1.01	0.14
Case type and origin						
Case type at the time of notification						
New case	1			1		
Relapse	1.07	0.99–1.14	0.07	1.07	0.99–1.14	0.08
Re-treatment after abandonment	1.09	1.01–1.18	**0.04**	1.17	1.08–1.27	**<0.001**
Re-treatment after antibiotic failure	0.96	0.76–1.21	0.72	0.99	0.78–1.24	0.90
Re-treatment after adverse events[a]	1.18	0.93–1.50	0.17	1.82	1.46–2.27	**<0.001**
Clinical presentation						
Extrapulmonary TB	1			1		
Pulmonary TB	1.07	1.01–1.13	**0.03**	1.11	1.05–1.18	**<0.001**
Diagnostic origin						
Active search at institutions	1			1		
Active search in the community	0.93	0.79–1.10	0.40	0.72	0.61–0.86	**<0.001**
Outpatient demand	0.96	0.87–1.06	0.43	0.91	0.82–1.01	0.08
Post-mortem (autopsy)	0.76	0.60–0.96	**0.02**	0.79	0.64–0.99	**0.04**
Contact tracing	0.78	0.67–0.92	**<0.001**	0.58	0.49–0.68	**<0.001**
Urgency/Emergency	0.83	0.74–0.93	**<0.001**	0.75	0.67–0.83	**<0.001**
During hospitalization	1.00	0.89–1.12	0.99	0.83	0.74–0.93	**<0.001**
No information	0.79	0.55–1.13	0.20	1.01	0.73–1.42	0.93
Intercept	0.91	0.79–1.06	0.22	0.90	0.78–1.04	0.15

OR, odds ratio. 2019/2020 model: Akaike's Information Criterion (AIC) and Bayesian Information Criterion (BIC) = null (−26,267.87), model (−26,193.51)—AIC: 52,445.01 and BIC: 52,692.79. Hosmer–Lemeshow chi2(8) = 6.11, P-value = 0.6344. 2019/2021 model: AIC and BIC = null (−26,447.73), model (−26,304.18); AIC = 52,666.29, BIC = 52,914.27. Hosmer–Lemeshow chi2(8) = 9.02, P-value = 0.3405. P-values in bold are considered statistically significant. [a]Re-treatment after change in treatment scheme due to adverse events.

Table 3: **Multiple logistic regression analyses of variables associated with tuberculosis (TB) notification in 2019 (pre-pandemic year) compared to 2020 (first year of the pandemic) or 2021 (second year of the pandemic) in the state of São Paulo, Brazil.**

institutions. This difference in diagnostic origin between both pandemic years is likely due to the improvement in post-mortem diagnostics with a concomitant decrease in diagnostics during hospitalizations and active search in the community in 2021 compared to 2020 (Table 1).

The odds of being reported as a tuberculosis case in 2020 were significantly higher among Black (OR = 1.1) and Pardo (OR = 1.07) individuals compared to white people, and among those with diabetes (OR = 1.09). The odds of being reported as a tuberculosis case in 2020 were also significantly higher among patients whose case type at notification was classified as "re-treatment after abandonment" (OR = 1.09) compared to those classified as "new cases", and among people with pulmonary tuberculosis (OR = 1.07) compared to those with extrapulmonary tuberculosis. These same variables also had an OR>1 statistically significantly in 2021 (Table 3), in addition to the odds being significantly higher among patients whose case type at notification was classified as "retreatment after change in scheme due to adverse events" (OR = 1.82).

Risk factors for death from tuberculosis

Risk factors for death from tuberculosis, compared to the "cure" outcome, were calculated separately for 2019 (pre-pandemic year) and 2020/2021 (pandemic years) (Table 4; Supplementary Table S4). In 2019 (pre-pandemic year), risk factors for death from tuberculosis included: male sex (OR = 1.48), age 20–49 (OR = 2.07), 50–69 (OR = 7.17) and ≥70 years-old (OR = 14.96), Black ethnicity/race (OR = 1.37), homelessness (OR = 2.75), mental illness (OR = 1.96), alcoholism (OR = 1.80), other immunological diseases (OR = 2.18), sputum culture in progress (OR = 5.00), sputum culture or HIV test not performed (OR = 1.50 or OR = 4.96, respectively) or without information (OR = 3.41 or OR = 8.73, respectively), self-administered treatment (OR = 1.84), having no information about treatment scheme (OR = 2.53), and case type at notification classified as "re-treatment after abandonment" (OR = 2.19) (Table 4). Individuals with no associated comorbidity (OR = 0.40), people deprived of liberty (OR = 0.33), and those with an X-ray not performed (OR = 0.63) or with no information (OR = 0.53) exhibited lower odds of death from tuberculosis (Table 4).

In 2020/2021 (pandemic years), the same risk factors detected in 2019 remained, except for Black ethnicity/race. Other risk factors emerged in 2020/2021: Pardo ethnicity/race (OR = 1.16), drug addiction (OR = 1.34), pulmonary tuberculosis (OR = 1.72), and "re-treatment after change in treatment scheme due to adverse events" (OR = 2.03). People deprived of liberty (OR = 0.25), individuals without associated comorbidity (OR = 0.44), and those with a negative sputum culture (OR = 0.71), an x-ray of suspected tuberculosis with cavity (OR = 0.81) or not performed (OR = 0.64) exhibited lower odds of death from tuberculosis (Table 4).

Discussion

During the pandemic years of 2020 and 2021, the number of tuberculosis cases notified in the state of São Paulo decreased by 10 and 8%, respectively. This finding indicates a lasting impact of the pandemic despite the introduction of COVID-19 vaccines in early 2021. In 2020, the detected decline in tuberculosis notifications was similar to the national average, which decreased by 10.16%.[23] In 2021, the state of São Paulo experienced a less pronounced decrease compared to the national average, specifically 8.1% compared to 11.3%.[23] Furthermore, the percentage declines observed in the state of São Paulo during 2020 and 2021 were lower than the global figures, which were 18.3% in 2020 and 9.8% in 2021.[3]

Our findings support previous research indicating that the SARS-CoV-2 pandemic worsened existing inequalities.[24,25] Accordingly, tuberculosis notifications of individuals with no education, HIV, drug addiction, and/or deprived of liberty were reduced during the pandemic. The –24.5% decrease in tuberculosis notifications among people deprived of liberty in 2021 suggests a significant impairment in case detection in this population. Another study showed a –7.6% reduction in tuberculosis notifications in Brazilian prisons in 2021 compared to the average number of cases per year between 2015 and 2019,[10] with the Southeast region, where São Paulo is located, reporting a –15.3% reduction. The difference seen with our study may be due to the inclusion of other states of the Southeast region and the comparison with the average of 2015–2019 instead of 2019 only. Nevertheless, the decline in tuberculosis notifications should motivate further studies to assess service performance and intensify case searches moving forward.

Brazil has the third-largest prison population globally,[26] with the state of São Paulo accounting for a quarter of this population.[27] A recent report showed that Brazil had the highest number of new tuberculosis cases among people deprived of liberty worldwide in 2019.[28] Fortunately, people deprived of liberty have one of the highest cure rates (80%–90%) reported among different population groups in São Paulo.[29,30] This high cure rate likely explains their lower odds for death due to tuberculosis. In contrast, there was a 68.0% increase in tuberculosis cases among prison system workers in 2021. These individuals are in close proximity to people deprived of liberty with tuberculosis and therefore face an elevated risk of infection.[31] It is reasonable to speculate that the failure to detect tuberculosis cases among incarcerated individuals during the pandemic contributed to a higher prevalence of the disease, subsequently increasing the risk of infection among prison staff.

During the pandemic, the reporting of diagnostic tests was compromised, with an increase in cases classified as "no information" for these tests. If a healthcare worker selects the "no information" option in the

Variables	2019			2020/2021		
	OR	95% CI	P-value	OR	95% CI	P-value
Sociodemographic variables						
Sex						
Female	1			1		
Male	1.48	1.17–1.90	**<0.001**	1.30	1.11–1.52	**<0.001**
Age group (years old)						
0–19	1			1		
20–49	2.07	1.12–4.33	**0.02**	2.21	1.47–3.50	**<0.001**
50–69	7.17	3.86–15.03	**<0.001**	5.36	3.55–8.50	**<0.001**
≥70	14.96	7.79–32.10	**<0.001**	13.94	9.00–22.53	**<0.001**
Ethnicity/race						
White	1			1		
Black	1.37	1.00–1.84	**0.05**	1.14	0.93–1.40	0.21
Pardo	1.18	0.95–1.47	0.14	1.16	1.00–1.34	**0.05**
East Asian descendants	1.46	0.65–2.89	0.34	1.11	0.61–1.90	0.73
Indigenous	0.70	0.01–6.17	0.80	3.67	0.63–13.27	0.13
Ignored	1.09	0.66–1.71	0.73	1.21	0.89–1.62	0.23
Population type according to address						
Fixed address	1			1		
People deprived of liberty	0.33	0.15–0.64	**<0.001**	0.25	0.15–0.39	**<0.001**
People experiencing homelessness	2.75	1.88–3.95	**<0.001**	2.47	1.93–3.14	**<0.001**
Comorbidities						
HIV (yes)	0.54	0.10–3.07	0.52	0.94	0.25–3.02	0.93
Mental illness (yes)	1.96	1.07–3.37	**0.029**	1.84	1.26–2.62	**0.002**
Diabetes (yes)	1.30	0.98–1.71	0.07	1.15	0.95–1.39	0.15
Alcoholism (yes)	1.80	1.41–2.30	**<0.001**	1.91	1.63–2.25	**<0.001**
Drug addiction (yes)	1.09	0.81–1.46	0.56	1.34	1.11–1.61	**0.002**
Smoking (yes)	0.81	0.65–1.02	0.07	0.95	0.82–1.10	0.49
Other immunological diseases (yes)	2.18	1.18–3.79	**0.014**	1.82	1.16–2.77	**0.011**
No associated comorbidity (yes)	0.40	0.29–0.55	**<0.001**	0.44	0.35–0.54	**<0.001**
Diagnostic tests and treatment						
Bacilloscopy						
Positive	1					
Negative	0.78	0.59–1.04	0.09	1.04	0.87–1.25	0.65
In progress	0.83	0.13–3.70	0.82	1.12	0.24–3.79	0.87
Not performed	0.86	0.68–1.10	0.24	0.89	0.76–1.04	0.14
No information	0.57	0.10–2.10	0.43	1.13	0.55–2.17	0.73
Sputum culture						
Positive	1					
Negative	0.77	0.52–1.12	0.18	0.71	0.54–0.92	**0.01**
In progress	5.00	2.35–10.00	**<0.001**	3.67	1.89–6.71	**<0.001**
Not performed	1.50	1.19–1.89	**<0.001**	1.46	1.26–1.70	**<0.001**
No information	3.41	1.72–6.30	**<0.001**	2.33	1.54–3.43	**<0.001**
X-ray						
Suspected TB	1			1		
Normal	0.80	0.48–1.29	0.37	0.73	0.50–1.04	0.08
Other pathology	1.68	0.77–3.28	0.18	1.26	0.68–2.17	0.45
Suspected TB with cavity	0.92	0.70–1.20	0.54	0.81	0.67–0.98	**0.03**
Not performed	0.63	0.46–0.84	**<0.001**	0.66	0.55–0.78	**<0.001**
No information	0.53	0.28–0.94	**0.03**	1.27	0.95–1.69	0.11
HIV test						
Negative	1			1		
Positive	0.36	0.06–1.73	0.24	0.12	0.03–0.41	**<0.001**
In progress	4.12	0.95–13.43	0.06	2.23	0.75–5.39	0.14
Not performed	4.96	3.77–6.49	**<0.001**	4.99	4.12–6.03	**<0.001**

(Table 4 continues on next page)

Variables	2019			2020/2021		
	OR	95% CI	P-value	OR	95% CI	P-value
(Continued from previous page)						
No information	8.73	4.59–15.87	**<0.001**	6.63	4.35–9.94	**<0.001**
Type of treatment						
Directly observed therapy	1					
Self-administered	1.84	1.47–2.30	**<0.001**	1.80	1.56–2.08	**<0.001**
No information	2.53	1.35–4.51	**0.005**	6.35	4.63–8.62	**<0.001**
Case type and origin						
Case type at the time of notification						
New case	1			1		
Relapse	1.13	0.78–1.58	0.51	0.99	0.78–1.25	0.96
Re-treatment after abandonment	2.19	1.47–3.18	**<0.001**	1.53	1.18–1.96	**<0.001**
Re-treatment after antibiotic resistance	1.90	0.50–5.19	0.30	0.69	0.19–1.79	0.48
Re-treatment after adverse events[a]	1.39	0.47–3.36	0.52	2.03	1.11–3.48	**0.02**
Clinical presentation						
Extrapulmonary TB	1			1		
Pulmonary TB	1.41	0.99–2.03	0.06	1.72	1.35–2.22	**<0.001**
Intercept	0.003	0.001–0.01	**<0.001**	0.004	0.002–0.01	**<0.001**

OR, odds ratio. 2019 model: Akaike's Information Criterion (AIC), null (6,200.4), model (3418.75) and Bayesian Information Criterion (BIC) = null (6208.14), model (3752.19). Likelihood ratio test = 912.4276 on 45 df, P-value <0.0001, n = 14,446. 2020/2021 model: AIC = null (12,652.84), model (7421.70). BIC = null (12,661.13), model (7777.53). Likelihood ratio test = 1952.917 on 46 df, P-value <0.0001, n = 24,031. P-values in bold are considered statistically significant. [a]Re-treatment after change in treatment scheme due to adverse events. Supplementary Table S5 contains the corresponding absolute numbers of each category.

Table 4: **Firth's logistic regression analyses of variables associated with death due to tuberculosis (TB) (compared to "cure" outcome) in 2019 (pre-pandemic year) and 2020/2021 (pandemic years) in the state of São Paulo, Brazil.**

system, it likely indicates uncertainty about the test being conducted rather than accidental omission (i.e. missing data), suggesting communication breakdowns and diagnostic service disruptions. Unfortunately, data on rapid molecular testing was unavailable for the study, yet the rate of molecular testing in São Paulo has remained steady over the years, accounting for around 20% of diagnoses.[32] It is unlikely that this number increased during the pandemic, as no specific policies were implemented to promote its use.

Two important findings of our study are the steady increase in tuberculosis cases among people with diabetes mellitus and change in treatment scheme due to adverse events since 2016. In addition to increasing the susceptibility to tuberculosis, diabetes mellitus leads to worse treatment outcome, more side-effects, and increased drug-toxicity during tuberculosis treatment.[33] Rifampicin enhances the metabolism of numerous drugs prescribed to individuals with diabetes, patients with tuberculosis and diabetes face elevated risk of liver and kidney toxicity, and isoniazid can worsen diabetic neuropathy.[33] Importantly, in 2019, the number of pills of the intensive phase with rifampicin, isoniazid, pyrazinamide and ethambutol for people with body weight higher than 70 Kg changed to five,[34] whereas previously, people with body weight higher than 50 Kg would take four pills, without weight distinction.[35] Since notifications of change in treatment scheme due to adverse events have been increasing since 2016, the interplay between treatment toxicity and diabetes, drug dosing, body mass index, and obesity needs further research. Notably, diabetes mellitus was also considered a risk factor for death from tuberculosis, as reported previously.[36]

Treatment abandonment and notifications of cases as "re-treatment after treatment abandonment" increased while the cure rate declined during the pandemic. A similar decline in the cure rate of tuberculosis due to the pandemic in all Brazilian regions was described previously.[7] These findings were accompanied by a decrease in directly observed therapy, which has been previously associated with higher cure rates in the state of São Paulo.[30] Taken together, these results indicate a significant impact of the pandemic on tuberculosis treatment adherence and on the ability of the health service to reach every patient under treatment.

As observed globally,[3] deaths due to tuberculosis increased during the pandemic in the state of São Paulo. Although tuberculosis deaths had increased 12.28% in 2017 compared to 2016, it remained relatively stable until 2019 when the pandemic began. The average number of deaths in 2019/2020/2021 was 798 per year. In contrast, the number of tuberculosis cases notified post-mortem was 210 per year. Tuberculosis is not the primary cause of death in all reported autopsies, but it seems that around 1/5 to 1/6 of the tuberculosis deaths are diagnosed post-mortem. This worrisome finding means that many patients are not being detected by the

tuberculosis program prior to death. The reduction in the number of tuberculosis diagnostics post-mortem, particularly in 2020, is due to a halt in autopsy services that occurred to protect pathologists from SARS-CoV-2 infection risk. Therefore, the actual number of tuberculosis deaths is likely underestimated.

If COVID-19 was the primary cause of death for a patient with tuberculosis, their outcome would be categorized as "death from another cause". There was only a slight increase in the number of deaths from another cause in 2020 compared to 2019. While we cannot disregard the possibility of patients with tuberculosis dying of COVID-19 and being classified as "death from tuberculosis", most patients with tuberculosis die during hospitalizations or following urgent care. Under the Brazilian universal health care system, the chances of getting COVID-19 diagnosed in these settings is high. Additionally, for the ~1/5–1/6 of tuberculosis deaths diagnosed post-mortem, misdiagnosis is unlikely.

Contrary to current knowledge, HIV positive individuals presented lower odds of dying from tuberculosis compared to HIV negative individuals. HIV positive patients who die of tuberculosis are classified as "death from another cause"; AIDS is their primary cause of death. Thus, the category "positive HIV test" only had six patients who died in 2019 and 13 that died in 2020–2021. Most likely these individuals should have been classified as "death from another cause" and not "death from tuberculosis". Therefore, using this category in the analysis led to a misleading detection of lower odds of death from tuberculosis in HIV positive individuals. In fact, a significant proportion of patients with tuberculosis with an outcome of "death from another cause" had a HIV positive test (353 out of 885 in 2019, 345 out of 903 in 2020, and 344 out of 884 in 2021).

Most patients with tuberculosis who died were diagnosed at urgency/emergency facilities or during hospitalization (~60%) and are reported as new cases. Patients with sputum culture "in progress" and HIV tests "not performed" were also at high risk of death, likely indicating mortality before tests were conducted or results became available. Therefore, for patients diagnosed pre-mortem, tuberculosis-related deaths often occur when patients seek healthcare at an advanced stage of their illness. Factors of extreme vulnerability, such as drug addiction, alcoholism, and homelessness,[37] likely contributed to this finding.

Black and Pardo races/ethnicities were identified as risk factors for tuberculosis-related deaths, consistent with previous studies in Brazil.[38] Additionally, Black and Pardo patients had a higher likelihood of being notified as tuberculosis cases during the pandemic years. In Brazil, Black and Pardo individuals face a higher likelihood of poverty and limited access to essential necessities, including healthcare, compared to white individuals.[39] Non-white populations were also at increased risk of death due to COVID-19.[40] It is imperative to conduct additional research to comprehend how structural racism contributes to the restriction of essential healthcare services in marginalized communities.

The study has limitations. The report regarding patients' ethnicity/race combines self-declaration and classification performed by healthcare workers, leading to potential misclassification. In addition, information about professional occupation and schooling may be difficult to obtain from certain patients, which resulted in >10% missing data. The options for professional occupation also do not cover all possibilities. Mental illness and alcoholism are other variables for which accurate diagnostics are not always available. Thus, caution should be exercised when analyzing results from these variables. In addition, there is always uncertainty regarding the randomness of the missing data for each variable. Therefore, it is possible that some of the results obtained with these analyses may not be generalized to the whole population of patients with tuberculosis enrolling in the program.

The TBWeb system lacks data on gender identity and sexual orientation, thus the impact of tuberculosis on the LGBTQIA+ community in São Paulo remains understudied. The transgender population in Brazil has been excluded from education, healthcare, and social assistance, being affected by extreme violence and stigma fueled by gender-related prejudice.[41,42] Additionally, the nationality or migration status of patients with tuberculosis were not made available for this study. São Paulo is home to international migrants who often experience social and economic vulnerability upon arrival in Brazil. In a recent study, international migrants had higher odds of treatment interruption.[43] The vulnerabilities faced by these individuals could increase the risk of tuberculosis infection.

In conclusion, the SARS-CoV-2 pandemic affected tuberculosis notifications and deaths differently among population groups, exacerbating inequalities. Treatment abandonment, loss of follow-up, and challenges in accessing healthcare led to increased mortality. Findings from this study can help guide strategies of recovery, focusing on those populations that are at extreme risk of infection and death. It can also serve for future pandemic preparedness.

Contributors

MCB, EAW and AMSG conceptualized the study. MCB and AMSG performed data curation. MCB and AMSG performed statistical analyses. EAW contributed to study design and provided guidance on statistical analyses. MCB and AMSG analyzed the resulting data and wrote the original draft. AABPL, MJPR, GMO, MLVO provided raw data, contributed to study design, and interpreted the resulting data after analysis. AMSG supervised the study and acquired funding. All authors reviewed and edited the manuscript.

Data sharing statement

Raw data without the identification of patients can be made available after IRB (institutional review board) approval for its use and upon request to the Tuberculosis Division, Center for Epidemiologic Vigilance "Prof Alexandre Vranjac", São Paulo State Secretariat of Health, Brazil. All other data from the analysis was made available in this manuscript.

Editor note

The Lancet Group takes a neutral position with respect to territorial claims in published maps and institutional affiliations.

Declaration of interests

The authors declare no competing interests.

Acknowledgements

We are thankful to all staff from the Tuberculosis Division, Center for Epidemiologic Vigilance "Prof Alexandre Vranjac", São Paulo State Secretariat of Health, Brazil.

Funding: MCB fellowship was provided by the National Council for Scientific and Technological Development (CNPq process: 130803/2021-9). The graduate program was funded by the Coordination for the Improvement of Higher Education Personnel (CAPES, 001). This work was funded by FAPESP (2016/26108-0, 2020/07251-2).

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lana.2024.100765.

References

1 World Health Organization. Pulse survey on continuity of essential health services during the COVID-19 pandemic. https://iris.who.int/bitstream/handle/10665/334048/WHO-2019-nCoV-EHS_continuity-survey-2020.1-eng.pdf?sequence=1. Accessed April 21, 2024.
2 Jeong Y, Min J. Impact of COVID-19 pandemic on tuberculosis preventive services and their post-pandemic recovery strategies: a rapid review of literature. *J Korean Med Sci*. 2023;38:e43. https://doi.org/10.3346/jkms.2023.38.e43.
3 World Health Organization. *Global tuberculosis report*; 2022. https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2022. Accessed April 21, 2024.
4 John Hopkins Coronavirus Resource Center. COVID-19 map. https://coronavirus.jhu.edu/map.html. Accessed September 25, 2023.
5 Ministério da Saúde do Brasil. Tuberculose 2023 [tuberculosis 2023]. *Bol Epidemiológico*; 2023. https://www.gov.br/saude/pt-br/centrais-de-conteudo/publicacoes/boletins/epidemiologicos/especiais/2023/boletim-epidemiologico-de-tuberculose-numero-especial-mar.2023. Accessed April 21, 2024.
6 Economic Commission for Latin America and the Caribbean. *Social panorama of Latin America*; 2019. https://www.cepal.org/en/publications/44989-social-panorama-latin-america-2019. Accessed April 21, 2024.
7 Berra TZ, Ramos ACV, Alves YM, et al. Impact of COVID-19 on tuberculosis indicators in Brazil: a time series and Spatial analysis study. *Trop Med Infect Dis*. 2022;7:1–19. https://doi.org/10.3390/tropicalmed7090247.
8 Souza CDF de, Neto ERD, Matos TS, et al. Bridging the gaps: investigating the complex impact of the COVID-19 pandemic on tuberculosis records in Brazil. *Trop Med Infect Dis*. 2023;8. https://doi.org/10.3390/tropicalmed8090454.
9 Souza MDR, Paz WS da, Sales VBDS, et al. Impact of the COVID-19 pandemic on the diagnosis of tuberculosis in Brazil: is the WHO End TB strategy at risk? *Front Pharmacol*. 2022;13:1–10. https://doi.org/10.3389/fphar.2022.891711.
10 do Nascimento DR, Serpa SF, Bezerra-Santos M, et al. The impact of the COVID-19 pandemic on TB diagnosis in the Brazilian prison population, 2020–2021. *Int J Tuberc Lung Dis*. 2023;27:688–693. https://doi.org/10.5588/ijtld.22.0666.
11 Maia CMF, Martelli DRB, da Silveria DMML, Oliveira EA, Martelli Júnor H. Tuberculosis in Brazil: the impact of the COVID-19 pandemic. *J Bras Pneumol*. 2022;48:4–5. https://doi.org/10.36416/1806-3756/e20220082.
12 Pelissari DM, Bartholomay P, Johansen FDC, Fredi A. Diaz-Quijano. Effect of COVID-19 pandemic on tuberculosis notification. *medRxiv*. 2022. https://doi.org/10.1016/j.ijtb.2021.08.007.
13 Silva LM, Da Silva GD, Silva ABO, et al. The tuberculosis scenario in Brazil: impacts of the COVID-19 pandemic on unreporting and discontinuity of treatment. *Brazilian J Health Rev*. 2022;5:21067–21081. https://doi.org/10.34119/bjhrv5n5-260.
14 Pontes TAA, Ramos RA, Scolaro JP, Tonin FS, Riveros BS, Wiens A. Evaluation of the epidemiological aspects and the impact of COVID-19 on tuberculosis notifications in São Paulo. *Rev Ciencias Farm Basica e Apl*. 2021;42:1–11.
15 Orfão NH, Andrade RL de P, Ruffino-Netto A, et al. Influence of COVID-19 on the notification of drug-resistant pulmonary tuberculosis cases. *BMC Infect Dis*. 2023;23:1–7. https://doi.org/10.1186/s12879-023-08463-x.
16 Borges TS, Santos AL dos, Osaki SC, Zago CHF. *Tuberculosis notifications in the pre-pandemic and pandemic period of COVID-19 in Paraná state*. 2023:1825–1844.
17 Dos Santos FL, Souza LLL, Bruce ATI, et al. Patients' perceptions regarding multidrugresistant tuberculosis and barriers to seeking care in a priority city in Brazil during COVID-19 pandemic: a qualitative study. *PLoS One*. 2021;16:1–19. https://doi.org/10.1371/journal.pone.0249822.
18 Souza LLL, Santos FL dos, Crispim J de A, et al. Causes of multidrug-resistant tuberculosis from the perspectives of health providers: challenges and strategies for adherence to treatment during the COVID-19 pandemic in Brazil. *BMC Health Serv Res*. 2021;21:1–10. https://doi.org/10.1186/s12913-021-07057-0.
19 Instituto Brasileiro de Geografia e Estatística. População do Estado de São Paulo–Cidades [Population of the State of São Paulo–Cities]. https://cidades.ibge.gov.br/brasil/sp/panorama; 2023. Accessed April 21, 2024.
20 Instituto Brasileiro de Geografia e Estatística. *População residente estimada. SIDRA–sistema IBGE recuperação automática [estimated resident population. SIDRA–IBGE System of Automatic Recovery]*; 2023. https://sidra.ibge.gov.br/pesquisa/estimapop/tabelas. Accessed July 7, 2023.
21 Li Y, de Macedo Couto R, Pelissari DM, et al. Excess tuberculosis cases and deaths following an economic recession in Brazil: an analysis of nationally representative disease registry data. *Lancet Glob Health*. 2022;10:e1463–e1472.
22 Lindoso AABP, Ribeiro MCVS, Oliveira EA de, et al. *Boletim Especial Tuberculose 2006 a 2020 da Secretaria de Saúde do Estado São Paulo [Special Bulletin of Tuberculosis from 2006 to 2020 from the Secretary of Health of the State of São Paulo]*; 2021. https://www.saude.sp.gov.br/resources/cve-centro-de-vigilancia-epidemiologica/areas-de-vigilancia/tuberculose/doc/boletim2021_especial_tuberculose.pdf. Accessed April 21, 2024.
23 Ministério da Saúde do Brasil. *Tuberculose 2022 [tuberculosis 2022]. Bol epidemiológico*; 2022. https://www.gov.br/saude/pt-br/centrais-de-conteudo/publicacoes/boletins/epidemiologicos/especiais/2022/boletim-epidemiologico-de-tuberculose-numero-especial-marco-2022.pdf. Accessed April 21, 2024.
24 Marmot M, Allen J. COVID-19: exposing and amplifying inequalities. *J Epidemiol Community Health*. 2020;74:681–682. https://doi.org/10.1136/jech-2020-214720.
25 de Souza CDF, Machado MF, do Carmo RF. Human development, social vulnerability and COVID-19 in Brazil: a study of the social determinants of health. *Infect Dis Poverty*. 2020;9:124. https://doi.org/10.1186/s40249-020-00743-x.
26 Walmsley R. *World prison population list*. 10th ed. International Centre for Prison Studies; 2013. https://www.prisonstudies.org/sites/default/files/resources/downloads/wppl_10.pdf. Accessed April 21, 2024.
27 Fórum Brasileiro de Segurança Pública. *Anuário Brasileiro de Segurança Pública de 2022 [Brazilian Year Book of Public Safety of 2022]*; 2022. https://forumseguranca.org.br/wp-content/uploads/2022/06/anuario-2022.pdf?v=5. Accessed April 21, 2024.
28 Martinez L, Warren JL, Harries AD, et al. Global, regional, and national estimates of tuberculosis incidence and case detection among incarcerated individuals from 2000 to 2019: a systematic analysis. *Lancet Public Health*. 2023;8:e511–e519. https://doi.org/10.1016/S2468-2667(23)00097-X.
29 Secretaria de Saúde do Município de São Paulo. *Boletim Tuberculose Cidade de São Paulo 2016 [Tuberculosis Bulletin of São Paulo City]*; 2016. https://www.prefeitura.sp.gov.br/cidade/secretarias/upload/saude/vigilancia_em_saude/arquivos/boletimTb_2016_menor.pdf. Accessed April 21, 2024.

30 Maria V, Galesi N, Fukasava S. Situação epidemiológica da tuberculose no estado de São Paulo [Epidemiological situation of tuberculosis in the state of São Paulo]. *BEPA*. 2015;12:13–20. https://docs.bvsalud.org/biblioref/ses-sp/2015/ses-36288/ses-36288-6194.pdf. Accessed April 21, 2024.

31 Grenzel ML, Grande AJ, Miranda Paniago AM, Pompilio MA, Maria do Valle Leone de Oliveira S, Trajman A. Tuberculosis among correctional facility workers: a systematic review and meta-analysis. *PLoS One*. 2018;13:1–11. https://doi.org/10.1371/journal.pone.0207400.

32 Coordenadoria de Vigilância em Saúde. *Boletim Epidemiológico–Tuberculose–Programa Municipal de Controle da Tuberculose da Cidade De São Paulo, 2020-2021 [Epidemiological Bulletin–Tuberculosis–Program for the Control of Tuberculosis of the City of São Paul, 2020-2021]*; 2021. https://www.prefeitura.sp.gov.br/cidade/secretarias/upload/saude/boletim_tuberculose_2020.pdf. Accessed July 12, 2023.

33 Crevel R van, Critchley JA. The interaction of diabetes and tuberculosis: translating research to policy and practice. *Trop Med Infect Dis*. 2021;6. https://doi.org/10.3390/tropicalmed6010008.

34 Ministério da Saúde do Brasil. *Manual de recomendações para o controle da tuberculose no Brasil de 2019 [Manual of recommendations for the control of tuberculosis in Brasil of 2019]*; 2019. https://bvsms.saude.gov.br/bvs/publicacoes/manual_recomendacoes_controle_tuberculose_brasil_2_ed.pdf. Accessed April 21, 2024.

35 Ministério da Saúde do Brasil. *Manual de recomendações para controle da tuberculose no Brasil de 2011. [Manual of recommendations for the control of tuberculosis in Brasil of 2011]*; 2011. https://bvsms.saude.gov.br/bvs/publicacoes/manual_recomendacoes_controle_tuberculose_brasil.pdf. Accessed April 21, 2024.

36 Arriaga MB, Araújo-Pereira M, Barreto-Duarte B, et al. The effect of diabetes and prediabetes on antituberculosis treatment outcomes: a multicenter prospective cohort study. *J Infect Dis*. 2022;225:617–626. https://doi.org/10.1093/infdis/jiab427.

37 Ranzani OT, Carvalho CRR, Waldman EA, Rodrigues LC. The impact of being homeless on the unsuccessful outcome of treatment of pulmonary TB in São Paulo State, Brazil. *BMC Med*. 2016;14:1–13. https://doi.org/10.1186/s12916-016-0584-8.

38 De Viana PVS, Gonçalves MJF, Basta PC. Ethnic and racial inequalities in notified cases of tuberculosis in Brazil. *PLoS One*. 2016;11:1–16. https://doi.org/10.1371/journal.pone.0154658.

39 Instituto Brasileiro de Geografia e Estatística. *Desigualdades sociais por cor ou raça no Brasil. [Social Inequalities by Color or Race in Brazil]*; 2019. https://biblioteca.ibge.gov.br/visualizacao/livros/liv101681_informativo.pdf. Accessed January 22, 2020.

40 Li SL, Pereira RHM, Prete CA, et al. Higher risk of death from COVID-19 in low-income and non-white populations of São Paulo, Brazil. *BMJ Glob Health*. 2021;6:1–11. https://doi.org/10.1136/bmjgh-2021-004959.

41 Reisner SL, Poteat T, Keatley JA, et al. Global health burden and needs of transgender populations: a review. *Lancet*. 2016;388:412–436. https://doi.org/10.1016/S0140-6736(16)00684-X.

42 Gomes SM, Jacob MCM, Chaves VM, et al. Food insecurity in a Brazilian transgender sample during the COVID-19 pandemic. *PLoS One*. 2023;18:1–12. https://doi.org/10.1371/journal.pone.0284257.

43 Pinto PFPS. *Tuberculosis in internal and international migration in the state of São Paulo: similarities and contrasts*; 2020. https://www.teses.usp.br/teses/disponiveis/6/6141/tde-09032021-161952/pt-br.php. Accessed April 21, 2024.