The impact of the COVID-19 pandemic in tuberculosis preventive treatment in Brazil: a retrospective cohort study using secondary data

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Summary

Background Disruptions in tuberculosis services have been reported around the world since the emergence of the COVID-19 pandemic. However, the pandemic's effect on tuberculosis preventive treatment (TPT) has been poorly explored. We compared TPT-notified prescriptions and outcomes before and during the pandemic in Brazil.

Methods Retrospective cohort using secondary data from the Brazilian TPT information system in five cities with over 1000 notifications. The number of TPT prescriptions was analysed from 6 months after healthcare workers' training, in 2018, to July 2021. The proportion of TPT outcomes by the date of treatment initiation was analysed up to the end of 2020, as most outcomes of TPT started in 2021 were still unknown in July 2021. Joinpoint regression was used to evaluate trends.

Findings 14,014 TPT prescriptions were included, most from São Paulo (8032) and Rio de Janeiro (3187). Compared to the same epidemiological weeks in 2019, the number of TPT prescribed in 2020 increased in Rio de Janeiro (82%) and São Paulo (14%) and decreased in Recife (65%), Fortaleza (31%) and Manaus (44%). In 2021, however, there was a 93% reduction in TPT prescriptions in all cities. The proportion of completed TPT remained constant (median = 74%).

Interpretation The COVID-19 pandemic in Brazil was associated with a dramatic decrease in TPT prescriptions in 2021. Treatment adherence remained constant, suggesting that health services were able to keep people on treatment but did not perform well in providing opportunities for people to enter care. Efforts are needed to expand access to TPT.

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Keywords: SARS-CoV-2; Coronavirus; Tuberculosis; Isoniazid; Rifampicin; Syndemic

Introduction

In 2020, although 9.9 million new tuberculosis (TB) cases were estimated by the World Health Organization (WHO),[1] only 5.8 million were notified, as a consequence of disrupted TB services and reduced access to health services during the COVID-19 pandemic. This represents a 9-year setback.[2–4] Models project at least 1.85 (1.40–2.40) million additional deaths from TB in the coming years as a consequence of undiagnosed TB.[2,3] Brazil, one of the 30 high TB-burden countries, with around 70,000 new cases reported yearly,[1,3] is among the 16 countries that contributed the most to the reduction in the notification of cases during the pandemic.[1] In 2021, São Paulo (23%), Rio de Janeiro (17%), (Pernambuco) (7%), Ceará (4%) and Manaus (4%) concentrated more than 50% of TB cases.[5] Preliminary data suggest a 10.16% reduction (93,208 to 83,741)[6] in the number of notifications (new cases and retreatments) from 2019 to 2020 in the country,[6,7] and an 11.30% decrease (93,208 to 82,680) from 2019 to

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Research in context

Evidence before this study

Disruptions in tuberculosis services have been observed around the world since the emergence of the COVID-19 pandemic. However, the effect of the pandemic on tuberculosis preventive treatment (TPT) has been poorly explored. We searched for articles related to TPT and COVID in PubMed database. Out of the 98 titles retrieved, 17 were selected for abstract review; six of them for full text reading. Only two discussed the public health impact of the pandemic on TPT initiation and completion. Two additional studies were found in the list of references. Three studies report on TPT initiation rates and one in TPT completion; all four are retrospective cohorts from the United States of America (USA), Canada (n = 2) and Ethiopia. The USA cohort consists of 312 participants from one single TB clinic and did not find reductions in TPT initiation (56% vs. 64%, p = 0.28) or in treatment completion (65% vs. 63%, p = 0.85) in 2019 and 2020. However, in Ethiopia, a low-income country with a high TB burden, routinely collected data from 1448 children contacts (under 15 years of age) found reductions of up to 57% in TPT initiation comparing the same trimesters before and during the pandemic. This reduction had dropped to 1% in the first trimester of 2021, showing partial recovery. The two other studies were carried out in Canada, a high-income low TB-burden country. There was also a decrease in the average number of patients initiating TPT weekly in the Montreal Chest Institute cohort of 6849 persons, 11 vs. 5, a 59% reduction (p < 0.001). A Canadian multicentre 15-year cohort with over 8685 individuals that included the Montreal Chest Institute cohort and two other centres confirmed a decrease of up to 66% 28-months after the pandemic. Altogether, these cohorts suggest that the pandemic had a negative impact in treatment initiation both in high- and low-income settings, but treatment completion was poorly evaluated.

Added value of this study

We evaluated the impact of the COVID-19 pandemic on TPT prescription and outcomes by analysing secondary data from the Brazilian Ministry of Health TPT information system (IL-TB). Unlike the previous studies, Brazil is an upper-middle-income country with a high TB burden. It also had the second-highest COVID death poll. We included cities with at least 1000 notifications. Five capitals (out of 27, including the federal district) with 14,014 TPT notifications from 2018 until July 2021 fulfilled the inclusion criteria. In this largest cohort explored up to now, we observed a 93% reduction in overall notifications up to July 2021, compared to the same period in 2019. Importantly, however, the percentage of TPT completed among those who received a prescription was maintained. Although TPT notification is not mandatory, and despite including only five capitals, our study comprised 83% (14,014/16,866) of the TPT notifications in the database. Therefore, we believe that, even with such limitations, our findings have relevant implications for responding to future pandemics.

Implications of all the available evidence

Although the pandemic and consequent restriction measures adversely affected TPT initiation, the percentage of treatments completed among patients prescribed TPT is not impacted. These findings indicate that treatment adherence is maintained since the start of TPT, fostering the need to increase referrals for TB infection treatment and warrant entry to TB preventive services.

2021.[6] Some places of the country have reported even higher reductions of notifications in 2020.[8]

By July 2022, Brazil had notified over 33 million confirmed COVID-19 cases, the third country with the highest number of cases, and over 675,000 deaths, corresponding to 10.6% of the global COVID-19 death toll, the second country in the ranking. This corresponds to a mortality rate of 313 per 100,000 inhabitants in the 2-year period.[9,10] Despite these alarming numbers, there was never a complete lockdown in the country. Different states and municipalities responded to the pandemic with varying degrees of restrictions.[11]

TB preventive treatment (TPT) is one of the most effective strategies to eliminate the disease.[12] Unfortunately, we did not meet the UN High-Level Meeting commitment to offer 30 million TPT by 2022.[13] In a comprehensive review of the impact of the pandemic on TPT, few studies were found.[14] The impact of the COVID-19 pandemic on TB prevention has been poorly explored,[15–20] although preliminary data indicate a reduction of TPT prescription and uptake.[1,17,19,20]

The Brazilian Ministry of Health (MoH) recommends TPT notification since 2014. In 2018, the MoH implemented the "IL-TB" online TPT information system.[21] Persons with any indication to start TPT and who were prescribed any regimen are notified in this system, although notification is not mandatory, and some small cities still use printed forms to notify TPT (which are later digitized by the municipal TB program).[22–24] The MoH had gradually trained nurses, nurse aids and medical doctors of nine cities before the beginning of the pandemic. Training was conducted in person and lasted for two days. In this study, we compared the notifications of TPT prescription and outcomes from the information system in these 9 cities before and during the pandemic in Brazil.[6] Later, other cities were trained virtually and started using the system as well, but they were not included in this analysis.

Methods

Study design

This is a retrospective cohort study based on secondary routinely collected data.

Setting

Brazil recommends TPT for contacts of persons with pulmonary TB of any age, person living with HIV (PLH) and other high-risk groups.[25] TPT should only be offered to those with a positive tuberculin skin test (TST) or interferon-gamma release assay, with a few exceptions, such as PLH with a CD4+ cell count <350/mm^3 or PLH exposed to a TB index patient. In these situations, they are offered TPT regardless of any TB infection (TBI) test.[26] A chest radiogram to exclude active or subclinical disease is mandatory for all groups before prescribing TPT.[25] Until June 2021, only three TPT regimens were available in Brazil: 6 months of isoniazid (6H), 9 months of isoniazid (9H) or 4 months of rifampicin (4R).[25] The choice of isoniazid regimens (6H or 9H) depends on patients' and doctors' preferences, and 4R is recommended for children under 10 and adults over 50 years of age, those with liver disease and those with intolerance or presumed resistance to isoniazid. Treatment is considered completed, according to the MoH, if 80% of doses are taken in up to 24 weeks for 4R, 36 weeks for 6H and one year for 9H.[24,27,28] Notification of TPT is not mandatory, but it is recommended by the Brazilian National TB Program (NTP). In large cities, this can be done directly in the electronic platform by the healthcare worker. In smaller cities with non-computerised clinics, notification provided in written form and digitalised by the TB municipal program. Except for two states in the country, all other 25, including the Federal District, use this integrated information system.

With regards to the COVID-19 pandemic, the first case was reported on February 26, 2020 in Brazil.[5] A first wave was observed in 2020, with 7.6 million cases and 194,000 deaths. Vaccination started on January 18, 2021,[29] and the second wave, with 14.6 million cases resulted in 423,000 deaths in 2021. The third wave, in 2022, computed 10.9 million cases and 56,000 deaths up to July 2022, mainly due to the Omicron variant and its subvariants.[30]

The lack of articulation promoted by the Brazilian federal government regarding the establishment of effective coping strategies (e.g., lockdown and mass testing) compromised the response to the pandemic. As a consequence, states and municipalities had to adopt their own recommendations regarding social restrictions, leading to heterogeneities in the local responses to the pandemic. Technical standards were published reinforcing the need for the inclusion of testing for the detection of COVID-19, use of telemedicine and increase in hospital beds.[31] However, these efforts were not sufficient and the health system collapsed as evidenced by the abrupt increase in mortality, mainly due to the insufficient number of hospitals and ICU beds.[32]

Eligibility

The analyses were performed by periods of two weeks and by city, as the pandemic and the response to it followed different courses in different parts of the country. We arbitrarily defined a minimum number of 1000 notifications per city as the inclusion criteria since, with lower numbers, many periods without any notifications would occur, and results would be difficult to interpret.

Outcomes

We evaluated the following indicators as the outcomes: number of TPT prescribed, number of completed treatments (on the week of completion) and proportion of different treatment outcomes (according to the week of prescription).

Study period

The initial date for TPT notification was set at 24 weeks after the date of the first training, to allow full implementation of TPT policy. Training started in different calendar dates for the five cities included (Fortaleza, Manaus, Recife, Rio de Janeiro, and São Paulo). The earlier training occurred in Rio de Janeiro [epidemiologic week 16, 2018] and the last in Manaus (epidemiologic week 14, 2019). TPT notification started to be recorded as early as epidemiologic week 42, 2018 for Rio de Janeiro, and as late as epidemiologic week 40, 2019, for Manaus. Data until 19 July 2021 were available and analysed for prescriptions and number of completed treatments at the day of completion. For percentage outcomes of prescribed treatments, we excluded those who were possibly still under treatment (see definition below). Because most outcomes of TPT that started in 2021 were still open (no outcome recorded) in the database, we limited the analysis of proportion of outcomes to TPT started up to the end of 2020.

Data source and variables

The anonymized "IL-TB" database was obtained from the MoH in July 2021. Variables used in this study were city of treatment, drug prescribed (duration of prescribed treatment is not available in the system), date of prescription, date of treatment completion/interruption, treatment outcome, number of doses taken (for those with a final treatment outcome informed) and date of treatment outcome digitation. The following treatment outcomes are available in the IL-TB database: treatment completed, loss to follow up, transfer out, death, active TB during TPT, adverse events resulting in treatment interruption and TPT suspension when a new-born of a contagious mother is TST negative after three months of TPT. According to WHO, loss to follow-up is defined when the patient does not start treatment (primary loss

to follow up) or when treatment is interrupted for more than two consecutive months.[1]

Analysis

For individuals with missing outcomes, we attributed two TPT outcomes: probable loss to follow up or possibly still under treatment. Patients were considered possibly still under treatment according to the drug prescribed and the time recommended for treatment completion. We based our estimation on the literature recommendation.[33] Individuals would be allowed to complete treatment in 120% of the recommended duration of treatment regimen. For rifampicin, we considered up to 144 days (120*120%). For isoniazid, since there are two regimens, we considered the longest regimen, 9 months, to be conservative. Thus, 324 days were allowed (270*120%). In addition, we allowed 90 extra days for data entry to be completed (corresponding to the 58th percentile of the distribution of time between the end of treatment and date of data entry—for those with a reported treatment outcome). Those possibly still under treatment were excluded from the outcome analysis. Probable loss to follow up was combined with informed loss to follow up in the analyses.

Data were described using the software RStudio Version 1.4.1106 (PBC), aggregated by 2 epidemiological weeks and per city. Absolute numbers were compared in different periods considering the same epidemiological weeks. Results are presented visually, in figures, by city. Proportions of all outcomes are presented in the 2-epidemiologic week period when treatment was prescribed, while number of completed prescriptions are reported on the weeks of their completion. To evaluate change in time trends, we used joinpoint regression (Joinpoint software, version 4.9.0.1, Statistical Methodology and Applications Branch, Surveillance Research Program, Division of Cancer Control and Population Sciences and National Cancer Institute). The permutation test model was used to define the number of joinpoint.[34] We present biweekly percentage change (BPC) and their 95% confidence intervals (CI, Supplementary Table S1). Finally, we compared the number of treatments notified before and during the pandemic (same epidemiological weeks in different years) using the t-test for a sample with normal distribution and the Wilcoxon test when the normality assumption was broken. Note that epidemiological weeks of comparison are not the same for all cities as training and data observation in cities are not exactly the same.

Ethics

Ethical approval was not necessary as this is an anonymized databank publicly available in Brazil.

Role of the funding source

The funder had no role in the study design, data collection, data analysis, interpretation, or writing of the report.

Results

The database contained information since 2018 on 16,866 TPT notified from only 45 municipalities in 12 states, of which, 14,942 (89%—Fig. 1) were from five cities that had notified over 1000 TPT: São Paulo (8033 TPT notifications, TB incidence rate (TB-IR) in 2020 = 60/100,000 population), Rio de Janeiro (3189 TPT notifications, TB-IR = 110/100,000 population), Recife (1457 TPT notifications, TB-IR = 138/100,000 population), Manaus (1210 TPT notifications, TB-IR = 123/100,000 population) and Fortaleza (1053 notifications, TB-IR = 68/100,000 population). Of these, 928 were from prescriptions outside the study period and were excluded. Thus, 14,014 (83%) TPT notifications were considered in the analyses (Fig. 1).

The training activities were completed in Rio de Janeiro on 19 April 2018, in São Paulo on 23 May 2018, in Recife on 30 October 2018, in Fortaleza on 25 January 2019 and in Manaus on 2 April 2019. Mean time of observation before the start of the pandemic was 20 (±18) weeks. Being a contact of index TB patients was the most frequent indication for TPT (8955, 64%), followed by HIV infection (2275, 16%) and use of immunosuppressants drugs (1302, 9.3%) (Supplementary Fig. S1).

Number of prescriptions notified

Out of the 14,014 included notifications, 7446 (53%) were from women, overall mean age was 33.7 (±20.8) years, 8248 (59%) were self-declared black or mixed race, 33% were white. Isoniazid was prescribed for 13,692 (98%). Compared to the same epidemiological weeks in 2019, during the first wave of the COVID-19 pandemic (2020) there was a 37% increase ($p = 0.003$) in the number of TPT prescriptions, mainly due to an 82% increase in Rio de Janeiro ($p = 0.001$, Fig. 2, left column) and 14% in São Paulo ($p = 0.180$). Recife and Manaus showed a significant reduction in TPT prescriptions (65%, $p < 0.001$ and 44%, $p = 0.006$, respectively), while a non-significant reduction was observed in Fortaleza (31%, $p = 0.067$). In 2021, however, there was a substantial decrease in overall TPT notification (93% decrease, $p = 0.001$).

All cities presented significant BPC points for TPT notifications, at different moments (Fig. 2, left column and Supplementary Table S1): two in Recife, Fortaleza and Manaus (Fig. 2c–e), five in Rio de Janeiro (Fig. 2a) and four in São Paulo (Fig. 2b). In Rio de Janeiro (Fig. 2a), after an initial increase during the first wave, a substantial reduction was observed during the second wave. A similar pattern of initial increase followed by a sharp decrease was observed in the other cities, details are displayed in Supplementary Table S1. These results are consistent with reductions already identified in Brazil.[35]

Number of completed treatments

During the study period, 7052 subjects completed treatment. The number of completed treatments was

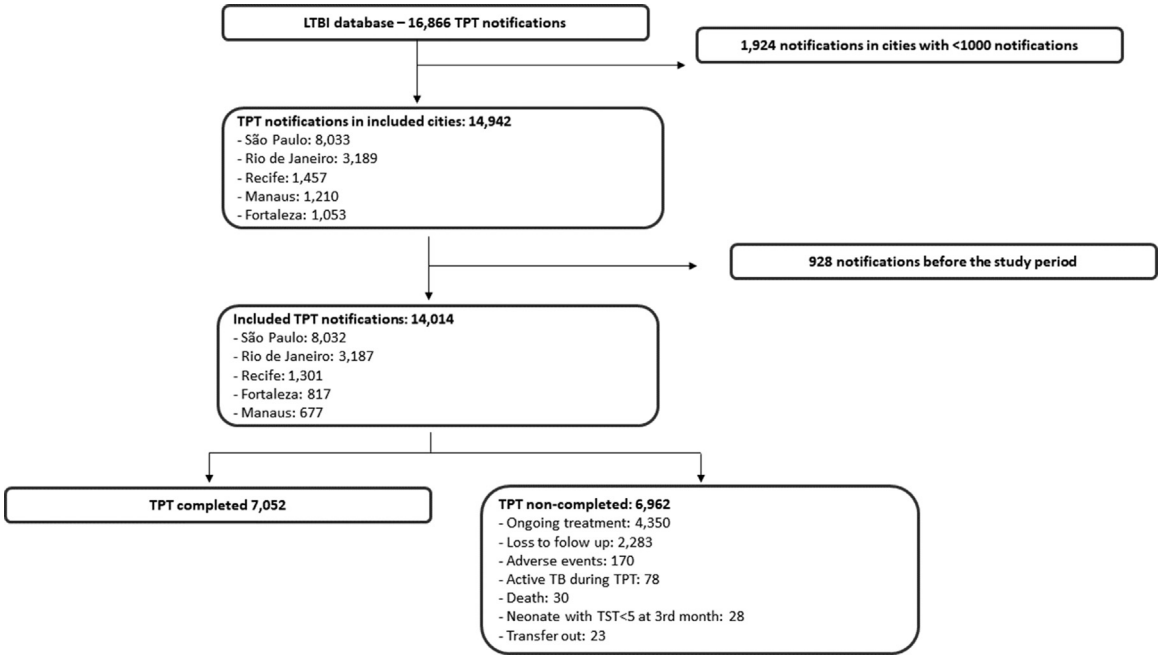


Fig. 1: **Flow diagram of included registers.** LTBI: Latent Tuberculosis Infection; TPT: Tuberculosis Preventive Treatment.

steady until the end of 2020, except for Rio de Janeiro, where there were fluctuations.

Proportion of outcomes according to the date of TPT prescription

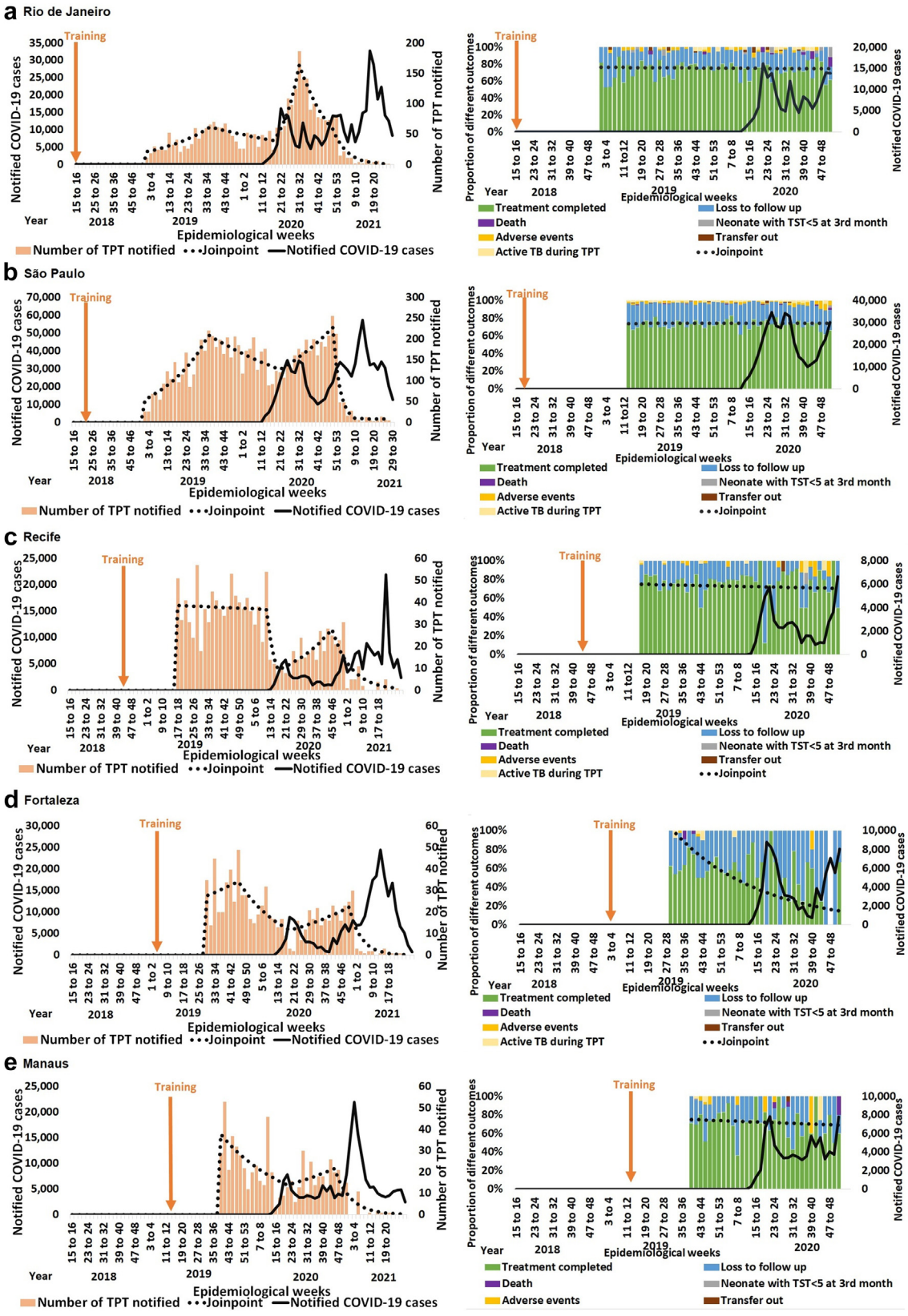
Of the 14,014 notifications, there are 4441 registries without outcome information. Among them, we estimated (from the rules described in the methods) two groups of outcomes: 4350 (98%) were considered possibly still under treatment and excluded from the analysis and the remaining 91 were considered loss to follow up. Among 9664 with an outcome (excluding patients undergoing treatment), 7052 (73%) completed treatment. Summing the total number of losses to follow up was 2283 (24%). The mean proportion of completed treatment varied from 51.40% to 75.31% across cities. The proportion of treatment completion was maintained over time for those starting TPT in all cities except for Fortaleza (BPC = –5.10, p = 0.031, Supplementary Table S1, right column), as shown by the absence in most of significant change points in the joinpoint line of completed TPT (Fig. 2, right column and Supplementary Table S1).

Discussion

In the present study, data from the Brazilian MoH indicates that the second wave of the pandemics in Brazil was accompanied by a dramatic drop in TPT prescriptions, which we did not see in a primary analysis of TB notifications (Supplementary Fig. S2). The reduction was substantially sharper than the decrease of TB disease notifications, which had dropped by 11.30% in 2021.[6] Thus, the decrease in the numbers of TB patients alone does not explain this dramatic drop in TPT prescriptions. However, the proportion of treatment completed remained steady, indicating that, although provision of service to new individuals was disrupted, those who were already included in the health system were able to acquire medication and finish their course of TPT. Although only part of the prescribed TPT is reported in the database, as TPT notification is not mandatory and many cities did not use the information system in the study period, we have no reasons to believe that the same phenomena was not observed for non-notified TPT.

The reasons for TPT prescription also changed during the pandemic. While 57% of prescriptions notified to this system are usually of contacts of index patients,[5] we found that contacts were a greater proportion (63%) of the records in our database during the pandemic, with a larger reduction among persons using immunosuppressive drugs (15%[5] vs. 9.3% in our database). Finally, as expected, the timing of the reductions was not the same in the different cities. Differences in the pandemic burden and in the response of local government may explain this heterogeneity, as the federal government never dictated any restrictions to the country.[11,36–39]

Globally, health services—including TB services—disruptions were reported by 40% of the countries that participated in a WHO study.[40] Of these countries, 66%


a Rio de Janeiro
b São Paulo
c Recife
d Fortaleza
e Manaus
Training
Notified COVID-19 cases
Number of TPT notified
Epidemiological weeks
Year
2018
2019
2020
2021
Number of TPT notified
Joinpoint
Notified COVID-19 cases
Proportion of different outcomes
Treatment completed
Death
Adverse events
Active TB during TPT
Loss to follow up
Neonate with TST<5 at 3rd month
Transfer out
Joinpoint

attributed disruption to medical leave or displacement of the workforce to COVID-19 services,[40] impacting tuberculosis indicators, including the number of notifications.[41] There was a partial recovery in many countries in 2021, with more susceptible and drug-resistant TB diagnoses then in 2020, but this is still below the pre-pandemic figures. Brazil is one of the countries that presented partial recovery.[42] Although less explored than TB diagnostic services, TBI diagnosis and TPT severe disruptions were reported in the USA,[13] Canada,[16,19] Ethiopia[20] and Mexico.[43] This is of crucial importance as disruption of TB preventive services may reverse years of progress in reducing TB incidence during the last decade. Fortunately, globally the number of TPT rebounded in 2021 to 2019 levels, but with the exception of PLH, we are still far from the 30 million we should have reached.[42]

Surprisingly, the number of prescriptions increased during the first pandemic wave in Rio de Janeiro. The high awareness of the importance of COVID-19 contact tracing[14] has resulted in more TB contacts identified in 2020, and may be an explanation for this finding. It is however not clear why the same phenomenon was not observed in other cities. Alternatively, it is possible that this increase reflects a delayed registration of previous prescriptions, due to overwhelmed healthcare services during the pandemics.

Delays in the reporting of treatment outcomes could also influence the high rates of completion and relatively low rates of loss to follow up. Nonetheless, we were very conservative when defining the periods for treatment completion and outcome digitation. With this approach, only 91 patients with no known outcome were considered loss to follow up. High rates of TPT completion during the pandemic are consistent with a smaller report from a single centre in Ohio, USA, a low-burden country.[17]

Our study has a number of limitations. Data was entered by hundreds of different nurses, nurse aids and medical doctors who have access to the system, thus, reporting quality may be heterogenous. Analyses were based on secondary data collected for a newly implemented system. It may take time until a surveillance system is fully operational. This is the reason why data inclusion started 6 months after training. Also, notifications are not mandatory and may have been considered a less relevant task during the pandemic, contributing to an artificial decrease in notifications. We selected the five cities with the highest numbers of notifications. The trends detected in these cities may not reflect the impact of the pandemic in smaller cities. As for the treatment, the database does not have a clear information on the regimen prescribed, only the drug is informed, thus a great proportion of patients were excluded from the outcome analyses. Additionally, data was available only until the second wave of the pandemic. The huge third wave due to the Omicron variant during 2022 may have had different effects on TB services. Nevertheless, preliminary data from the MoH suggests recovery of treatment prescriptions to previous levels after the end of the second wave.[5] Importantly, the information system only captures patients who were prescribed TPT. Losses in the previous steps of the cascade of care are not captured, thus data on TPT candidate identification and diagnosis cannot be analysed from this database. Finally, we did not control for other possible factors impacting TB services, such as primary care investment—unlikely during the pandemic crisis—or differences in response to the pandemic implemented by each city and state.

Despite these limitations, this is the first report of the impact of the pandemic in TPT services in an upper-middle-income and high TB/COVID-burden country. The sustained adherence to TPT suggests that more prescriptions are worth the effort, even in the middle of a sanitary emergency.

The impact of the COVID-19 pandemic on the reduction of TPT notifications reinforces the need for the monitoring of TB treatment indicators and the entire TB care cascade. Beyond tackling the direct impact of the pandemic, public health responses to any sanitary crisis need to ensure the maintenance of adequate health care for chronic and infectious diseases, including active and latent tuberculosis.

Contributors

AT was responsible for conceptualization, funding acquisition, supervision, project administration, formal analysis, and original draft writing. GW and IC have verified the data. IC contributed to the first draft writing and formal data analysis. GW oversaw methodological choices, formal data analysis and interpretation. All authors had access to all the data reported in the study, contributed to review & editing of the first draft, and approved the final version.

Data sharing statement

The database is available upon reasonable request to the corresponding author.

Declaration of interests

We declare no competing interests.

Acknowledgement

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Fig. 2: **Number of notified TPT (pink bars on the left), proportion of TPT outcomes by date of TPT initiation (coloured bars on the right) and number of COVID-19 cases reported (black line) during the pandemic in 5 Brazilian capitals.** TPT: Tuberculosis Preventive Treatment; TST: Tuberculin Skin Test; TB: Tuberculosis. *Treatment outcome shown on weeks of TPT prescription. For calculation of proportions, possibly ongoing treatments were excluded from the denominator. **The joinpoint in the right column refers to the complete treatment.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lana.2023.100444.

References

1 *Global tuberculosis report 2021*. Licence: CC BY-NC-SA 3.0 IGO. Geneva: World Health Organization; Oct 2021. https://www.who.int/publications-detail-redirect/9789240037021. Accessed November 1, 2021.

2 Glaziou P. Predicted impact of the COVID-19 pandemic on global tuberculosis deaths in 2020 [preprint]. *medRxiv*; 2020. https://www.medrxiv.org/content/10.1101/2020.04.28.20079582v1.

3 *Global tuberculosis report 2019*. Geneva: World Health Organization; 2019. Licence: CC BY-NC-SA 3.0 IGO. https://www.who.int/publications/i/item/9789241565714

4 Migliori GB, Thong PM, Alffenaar J-W, et al. Gauging the impact of the COVID-19 pandemic on tuberculosis services: a global study. *Eur Respir J*. 2021;58:2101786.

5 Brasil Ministério da Saúde, Secretaria de Vigilância em Saúde. Departamento de Doenças de Condições Crônicas e Infecções Sexualmente Transmissíveis – DCCI. Boletim Epidemiológico de Tuberculose https://www.gov.br/saude/pt-br/centrais-de-conteudo/publicacoes/boletins/epidemiologicos/especiais/2022/boletim-epidemiologico-de-tuberculose-numero-especial-marco-2022.pdf/view ;March 2022. Accessed June 10, 2022..

6 Brasil. Ministério da Saúde. *Secretaria de Vigilância em Saúde. Departamento de Doenças de Condições Crônicas e Infecções Sexualmente Transmissíveis – DCCI. Boletim Epidemiológico de Tuberculose – 2021*; 2021. published online March 1. http://www.aids.gov.br/pt-br/pub/2021/boletim-tuberculose-2021. Accessed November 5, 2021

7 Souza MDR, da Paz WS, 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;13:891711.

8 de Souza CDF, Coutinho HS, Costa MM, Magalhães MAFM, Carmo RF. Impact of COVID-19 on TB diagnosis in northeastern Brazil. *Int J Tuberc Lung Dis*. 2020;24:1220–1222.

9 Center for Systems Science and Engineering (CSSE). *COVID-19 dashboard*; 2022. published online Baltimore. https://www.arcgis.com/apps/dashboards/bda7594740fd40299423467b48e9ecf6. Accessed July 25, 2022

10 IBGE | Projeção da população. https://www.ibge.gov.br/apps/populacao/projecao/box_popclock.php. Accessed December 12, 2021.

11 Silva LLSD, Lima AFR, Polli DA, et al. Medidas de distanciamento social para o enfrentamento da COVID-19 no Brasil: caracterização e análise epidemiológica por estado. *Cad Saude Publica*. 2020;36:e00185020.

12 Dye C, Glaziou P, Floyd K, Raviglione M. Prospects for tuberculosis elimination. *Annu Rev Public Health*. 2013;34:271–286.

13 World Health Organization. A situational analysis of programmatic management of TB preventive treatment in the WHO South-East Asia region. https://www.who.int/publications-detail-redirect/9789290228059; 2020. Accessed May 28, 2022.

14 Trajman A, Felker I, Alves LC, et al. The COVID-19 and TB syndemic: the way forward. *Int J Tuberc Lung Dis*. 2022;26:710–719.

15 Aznar ML, Espinosa-Pereiro J, Saborit N, et al. Impact of the COVID-19 pandemic on tuberculosis management in Spain. *Int J Infect Dis*. 2021;108:300–305.

16 Saroufim M, Geric C, Mannix S, et al. Impact of COVID-19 pandemic on latent and active tuberculosis treatment registrations in Montreal, Canada: a retrospective study at the Montreal Chest Institute, Global Health Programs. https://www.mcgill.ca/globalhealth/article/global-health-night-2020-canada-americas-covid-19-global-health-programs-award-recipients/impact-covid-19-pandemic-latent-and-active-tuberculosis-treatment-registrations. Accessed January 1, 2022.

17 Stantliff TM, Houshel L. The latent tuberculosis infection cascade of care during the COVID-19 pandemic response in a mid-sized US city. *Open Forum Infect Dis*. 2021;8:S787.

18 Cronin AM, Railey S, Fortune D, Wegener DH, Davis JB. *Notes from the field:* effects of the COVID-19 response on tuberculosis prevention and control efforts — United States, March–April 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69:971–972.

19 Geric C, Saroufim M, Landsman D, et al. Impact of Covid-19 on tuberculosis prevention and treatment in Canada: a multicentre analysis of 10,833 patients. *J Infect Dis*. 2021;22:1317. jiab608.

20 Arega B, Negesso A, Taye B, et al. Impact of COVID-19 pandemic on TB prevention and care in Addis Ababa, Ethiopia: a retrospective database study. *BMJ Open*. 2022;12:e053290.

21 Ministério da Saúde, Sistema de Informação para notificação das pessoas em tratamento da infecção latente pelo Mycobacterium tuberculosis (IL-TB) | Departamento de Doenças de Condições Crônicas e Infecções Sexualmente Transmissíveis. Sistema de Informação para notificação das pessoas em tratamento da infecção latente pelo Mycobacterium tuberculosis (IL-TB), Aug 2022. https://www.gov.br/aids/pt-br/indicadores-epidemiologicos/sistemas-de-informacao/il-tb. Accessed October 27, 2022.

22 Ministério da Saúde. *Sistema de informação de agravos de notificação-tuberculose*; 2014. published online Oct 2. http://portalsinan.saude.gov.br/images/documentos/Agravos/Tuberculose/Tuberculose_v5.pdf. Accessed July 11, 2021

23 SITETB. Sistema de Informação de tratamentos especiais de tuberculose. http://sitetb.saude.gov.br/index.html.

24 Brasil Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Doenças de Condições Crônicas e Infecções Sexualmente Transmissíveis. In: *Protocolo de vigilância da infecção latente pelo* Mycobacterium tuberculosis *no Brasil*– 2. ed. Brasília: Ministério da Saúde; 2022.

25 Brasil Ministério da Saúde. Secretaria de Vigilância em saúde. Departamento de Vigilância das Doenças Transmissíveis. In: *Manual de Recomendações para o controle da tuberculose no Brasil. - 2. ed. -Brasília: Ministério da Saúde, 2019.Ministério da Saúde, Manual de recomendações para o controle da tuberculose no brasil*; 2019. https://bvsms.saude.gov.br/bvs/publicacoes/manual_recomendacoes_controle_tuberculose_brasil_2_ed.pdf. Accessed June 27, 2021.

26 Ministério da saúde. *Nota informativa No 11/2018-.DIAHV/SVS/MS*; 2018. published online Nov. http://azt.aids.gov.br/documentos/NOTA%20INFORMATIVA%20N%C2%BA%2011-2018%20-%20TRATAMENTO%20DA%20ILTV%20EM%20PVHIV.pdf

27 Centers for Disease Control and Prevention. *Tuberculosis (TB) - treatment regimens for latent TB infection*. Centers for Disease Control and Prevention; 2022. published online Feb 10. https://www.cdc.gov/tb/topic/treatment/ltbi.htm. Accessed June 14, 2022

28 Sterling TR. Guidelines for the treatment of latent tuberculosis infection: recommendations from the national tuberculosis controllers association and CDC, 2020. *MMWR Recomm Rep*. 2020;69:1. https://doi.org/10.15585/mmwr.rr6901a1.

29 Brasil Ministerio da Saude. OCTOGÉSIMO SEXTO INFORME TÉCNICO88ª PAUTA DE DISTRIBUIÇÃOPLANO NACIONAL DE OPERACIONALIZAÇÃO DA VACINAÇÃO CONTRA A COVID- 19ORIENTAÇÕES TÉCNICAS RELATIVAS À CONTINUIDADE DA CAMPANHA NACIONAL DE VACINAÇÃO CONTRA A COVID-19, 2022. https://www.gov.br/saude/pt-br/coronavirus/informes-tecnicos/2022/86o-informe-tecnico.pdf. Accessed July 3, 2022.

30 Ministério da Saúde. *Coronavírus Brasil*; 2022. published online July 18 https://covid.saude.gov.br/. Accessed July 18, 2022.

31 Machado CV, Pereira AMM, Freitas De CM. *Políticas e sistemas de saúde em tempos de pandemia: nove países, muitas lições. Série Informação para ação na Covid-19 | Fiocruz*; 2022. https://books.scielo.org/id/t67zr. Accessed October 14, 2022.

32 Fundação Oswaldo Cruz Instituto de Comunicação e Informação Científica e Tecnológica emSaúde. *Nota Técnica 22 de 9 de novembro de 2021. O "represamento" do atendimento em saúde no SUS*; 2021. https://www.arca.fiocruz.br/handle/icict/51248. Accessed October 14, 2022.

33 Menzies D, Adjobimey M, Ruslami R, et al. Four months of rifampin or nine months of isoniazid for latent tuberculosis in adults. *N Engl J Med*. 2018;379:440–453.

34 Selecting the final model. Joinpoint help system. https://surveillance.cancer.gov/help/joinpoint/tech-help/frequently-asked-questions/selecting-the-final-model. Accessed September 25, 2022.

35 Santos JCV, Orsi JSR, Ribeiro VS, Tuon FF, Telles JP. The challenging of HIV care 1 year after of coronavirus disease 2019 pandemic: results from a Brazilian cohort. *AIDS*. 2021;35:2069–2072.

36 Xavier DR, Silva ELE, Lara FA, et al. Involvement of political and socio-economic factors in the spatial and temporal dynamics of

COVID-19 outcomes in Brazil: a population-based study. *Lancet Reg Health Am*. 2022;10:100221. https://doi.org/10.1016/j.lana.2022.100221.

37 Burki T. No end in sight for the Brazilian COVID-19 crisis. *Lancet Microbe*. 2021;2:e180.

38 Zeiser FA, Donida B, da Costa CA, et al. First and second COVID-19 waves in Brazil: a cross-sectional study of patients' characteristics related to hospitalization and in-hospital mortality. *Lancet Reg Health Am*. 2022;6:100107. https://doi.org/10.1016/j.lana.2021.100107.

39 Henriques CMP, Vasconcelos W. Crises dentro da crise: respostas, incertezas e desencontros no combate à pandemia da Covid-19 no Brasil. *Estud Av*. 2020;34:25–44.

40 World Health Organization, Second round of the national pulse survey on continuity of essential health services during the COVID-19 pandemic. https://www.who.int/publications-detail-redirect/WHO-2019-nCoV-EHS-continuity-survey-2021.1; 2021. Accessed April 2, 2022.

41 Kim B, Kang YA, Lee J. Heterogeneous impact of Covid-19 response on tuberculosis burden by age group. *Sci Rep*. 2022;12:13773.

42 *Global tuberculosis report 2022*. Geneva: World Health Organization; 2022. Licence: CC BY-NC-SA 3.0 IGO. https://www.who.int/publications-detail-redirect/9789240061729. Accessed January 7, 2023

43 Muñiz-Salazar R, Le T, Cuevas-Mota J, et al. Impact of COVID-19 on tuberculosis detection and treatment in Baja California, México. *Front Public Health*. 2022;10:921596.