Nationwide economic analysis of pulmonary tuberculosis in the Brazilian healthcare system over seven years (2015–2022): a population-based study

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Summary

Background Tuberculosis (TB) remains a global challenge and disproportionately affecting vulnerable populations. This study analyses the economic burden of pulmonary TB in Brazil, focusing on direct healthcare costs. It also evaluates the cost-effectiveness of the Directly Observed Treatment (DOT) strategy and the economic effort required to achieve a 90% probability of cure.

Methods A nationwide retrospective study utilized data from the Brazilian Information System for Notifiable Diseases (SINAN) between 2015 and 2022. The cost per pulmonary TB case was estimated, encompassing expenses related to healthcare professionals, medication, laboratory exams, and the duration of treatment reported in SINAN. The population was stratified based on the presence of social vulnerabilities or a history of previous anti-TB treatment. Number Needed to Treat (NNT) analyses assessed the effectiveness of DOT implementation. Additionally, the study calculated the cost needed to achieve a 90% probability of cure through binomial regression models.

Findings The total direct cost for pulmonary TB in Brazil during the seven years exceeded $1.3 billion, with retreatment cases accounting for $23.5 million. The lowest NNT of DOT were homeless (3.0), people who use drugs (3.72), and retreatment (4.56) subpopulations. These groups also presented the highest cost to achieve a 90% probability of cure.

Interpretation This study highlights the economic impact of pulmonary TB on the Brazilian healthcare system. It underscores the effectiveness of DOT across various patient groups, regardless of their vulnerabilities or previous anti-TB treatment history. NNT analyses highlighted retreatment, homeless, and people who use drugs subpopulations as the most effective for DOT implementation.

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Keywords: Tuberculosis; Cost; Retreatment; Vulnerable populations; Direct observed treatment; Treatment outcome

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Research in context

Evidence before this study

We used PubMed and Embase to search for papers published in Portuguese and English between the period of database inception and January 5, 2024. Our search focused on papers assessing the direct cost of pulmonary tuberculosis cases, specifically within Brazil. Additionally, we sought studies that evaluated the cost-effectiveness of direct observed treatment, particularly in vulnerable populations characterized by social vulnerabilities and a history of anti-tuberculosis treatment. We employed search terms such as "tuberculosis" AND ("cost" OR "cost-effectiveness" OR "burden") AND "Brazil" AND ("treatment" OR "anti-tuberculosis therapy"). The research we found had limitations in its focus, primarily addressing individual cities or states instead of offering a thorough nationwide outlook. Moreover, the selected studies did not directly address the implementation of direct observed treatment and its impact on vulnerabilities concerning the cost required to achieve the world health organization cure standard.

Added value of this study

Our study adds substantial value to the existing evidence by providing an unprecedented comprehensive national-level analysis of the direct costs of pulmonary TB in Brazil. While previous research has delved into patient-level costs, a holistic examination of the economic impact at the country level still needs to be improved. By assessing the direct costs per pulmonary TB case, our study contributes novel insights into the economic burden, offering a basis for policy and intervention strategies at both the national and international levels.

Implications of all the available evidence

The implications of our study are far-reaching, both in practice and policy. By showing the economic burden of pulmonary TB, our findings underscore the importance of tailored strategies, especially for vulnerable populations and those with a history of previous treatment. The study advocates for the continued implementation of the direct observed treatment strategy and highlights the need for cost-effective interventions. In the broader context of existing evidence, our research emphasizes the urgency of optimizing TB control. These insights hold significant implications for the global health community and warrant further research to refine and expand the evidence base.

Introduction

Tuberculosis (TB) is a threat that transcends the boundaries of public health, casting a devastating impact on nations marked by inequality and poverty,[1] disproportionately affecting vulnerable populations.[2] The intrinsic link between TB and poverty exacerbates challenges for individuals and countries already grappling with precarious socio-economic conditions, such as low and middle-income countries.[1] Furthermore, TB constitutes a heavy burden for affected individuals and imposes significant costs on the national healthcare infrastructure.

Despite the extensive exploration of the catastrophic costs borne by persons with TB and their families,[3] a critical gap exists in our understanding of the actual expenses associated with the TB care cascade at the national level in low and middle-income countries. A recent study estimated 31.8 million TB-related deaths between 2020 and 2050, with projected economic losses of $17.5 trillion worldwide.[4] In this context, Brazil is renowned for being a middle-income country hallmarked by socio-economic disparities[5] and faces an accentuated challenge concerning the cost of TB, both for patients and the government. The combination of social inequalities and the financial burden of TB further amplifies the need for a comprehensive and targeted approach to address this challenge.

Furthermore, pursuing goals outlined in the World Health Organization (WHO) End TB Strategy, such as eliminating catastrophic costs immediately,[6] highlights the urgent need for concerted actions to reverse the projected trajectory of economic and public health impacts related to TB. Also, it is essential to underline the economic implications of public health policies, such as providing directly observed treatment (DOT)[7] and the impact on anti-TB treatment outcomes. In this context, it is imperative to consider not only the costs borne to patients but also the government expenses and associated vulnerable populations,[8] and retreatment cases are crucial to decision-making strategies and to optimize resource allocation in public health policies.[9]

In the present study, we performed a retrospective study of all the TB cases reported in the Brazilian Information System for Notifiable Diseases (SINAN-TB) between 2015 and 2022 and employed health economic analysis techniques to study the costs and resources necessary for the fight against TB. We aimed to (1) estimate the direct cost of pulmonary TB in Brazil, (2) test the impact of DOT on the cost of pulmonary TB care and the relation between such cost and the anti-TB treatment outcomes, and (3) assess the monetary effort to achieve the standards of cure proposed by the WHO according with the presence of social vulnerabilities and previous history of TB treatment.

Methods

Study design

The methodology involved determining the cost of each case within the healthcare system and comparing

scenarios with and without DOT. Subsequently, we stratified the population based on a history of TB treatment and social vulnerabilities, including homeless individuals, pregnant women, healthcare workers, people deprived of liberty, people who use drugs, immigrants and people living with HIV. We then analysed outcomes and the cost per patient required to achieve the probability of cure advocated by the WHO.

The study incorporated the calculation of the Number Needed to Treat (NNT) to identify optimal populations for applying DOT. Multivariate models were employed to determine the cost per patient needed to meet the WHO cure standards within each subgroup. The study included all individuals diagnosed with TB in the SINAN-TB database from 2015 to 2022. The non-vulnerable group comprised cases reported without characteristic vulnerability at diagnosis, new cases, and those undergoing retreatment. We excluded children and adolescents (under 18 years old) from our analysis to ensure homogeneity, as the treatment for this group involves a different drug regimen that varies significantly with weight and age. However, weight is not reported on the notification forms and is not available in the database. Cases lacking information about outcomes (incomplete cases) and non-treatment-related outcomes were also excluded. Additionally, patients entering the system without information about previous TB treatment (Entry mode variable: post-mortem diagnosis) were excluded from the analysis. Of note, cases reported as cure with less than 30 days of treatment were also excluded of the analysis (Fig. 1).

Data collection

Adults (≥18 years old) with pulmonary TB in the SINAN-TB database during the study period were included. The details on how TB cases are notified in Brazil are described in the Supplementary Methods. TB was diagnosed by microbiologic confirmation (acid-fast bacilli in sputum smears or positive culture), chest radiography or histopathology, or clinical manifestations, according to the parameters established by the Manual of Recommendations for TB Control in Brazil (Brazilian TB guideline).[10] In addition to the type of TB diagnosis, SINAN-TB also stores data on patient characteristics, including clinical (diabetes, acid-fast bacilli in sputum smear samples, and TB culture) and epidemiologic (birth sex, age, substance consumption habits, and anti-TB treatment outcome) data. All variables used in this study are detailed in Table 1.

Entry mode definition

Entry mode is how the patient is notified in the government system, which depends on previous TB history. New case: those without a history of TB treatment, including any patient who has never undergone TB treatment or has done so for ≤30 days. Retreatment after loss to follow-up (LTFU): patient with a history of interruption of TB treatment for >30 days. Recurrence: a case with a previous history of TB cure. Post-mortem: cases identified late, i.e., at the time of or after the patient's death. We considered the retreatment cases (retreatment after LTFU and recurrence) for the analysis. We excluded transferred and post-mortem cases from the study due to the lack of information about previous TB history and TB treatment outcomes.

Outcome definition

An unfavourable outcome was defined as TB treatment failure (positive sputum smear results remain until the end of treatment), LTFU (if the patient has taken >30 consecutive days to return to a treatment unit after the expected return date), or death (the knowledge of a patient's death during treatment), while a favourable treatment outcome was defined as cure (clinical and bacteriologic). The definitions for a clinical or bacteriological cure, as well as for each specific unfavourable outcome, were determined following criteria found in the Manual of Recommendations for the Control of TB in Brazil and are depicted in detail in Supplementary Table S1.[10] Registries of other outcomes such as transferred (patient sent to another healthcare unit to finalize the treatment), treatment modification (factors that cause treatment modification: due to drug-resistant TB), change in diagnosis (patient diagnosed with another disease other than TB), and "ongoing treatment," were excluded from the analyses due to the lack of information on the final treatment outcome (Fig. 1). Characteristics of the overall population included in the study is provided in Supplementary Table S2. Characteristics of each subpopulation included in the study is provided in Tables 1 and 2.

Vulnerability definition

In accordance with the WHO, we defined vulnerable populations as groups who have an increased risk of developing active TB. The vulnerabilities evaluated in this study were pregnancy,[10] healthcare work,[11] incarceration,[12] homelessness,[2,13] drug use,[10] living with HIV,[10] and immigration[14] at the time of diagnosis. We did not consider people who use alcohol or tobacco as specific vulnerable populations because of overlap with the vulnerability groups included. Instead, alcohol and tobacco use were used as variables to characterize the subpopulations and were included among factors used to adjust association analyses.

Directly observed treatment definition

DOT is a recommended strategy to enhance medication adherence, specifically for TB treatment. It involves the daily medication intake under the observation of a healthcare professional (most of them were community health agents or nurses). For a regimen to be considered DOT, it requires a minimum of three observed medication intakes per week by a community health agent.[7]

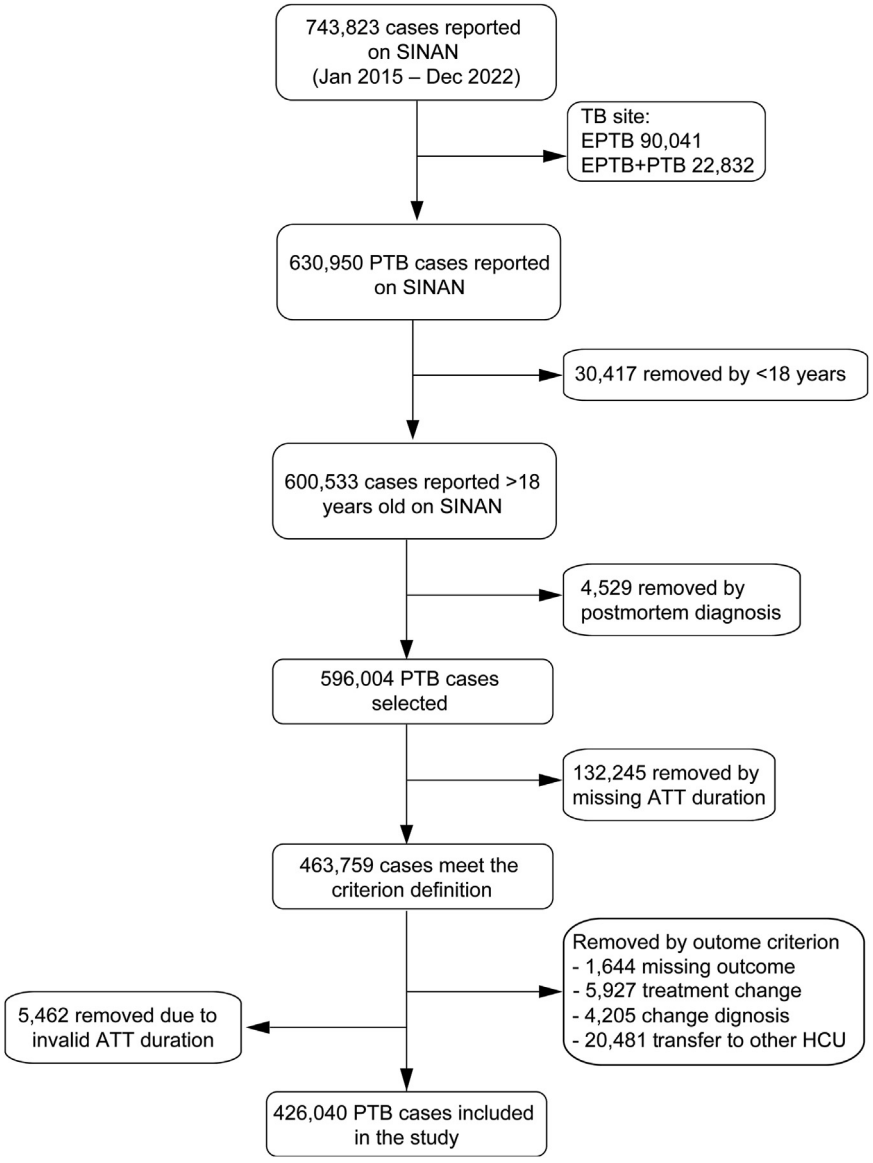

***Fig. 1:* Flow chart of the TB cases notified in Brazil between 2015 and 2022 included in the study.** Abbreviations: SINAN: Brazilian Information System for Notifiable Diseases; PTB: pulmonary tuberculosis; EPTB: extrapulmonary tuberculosis, ATT: anti-tuberculosis treatment; HCU: healthcare unit.

Within the SINAN-TB, since 2014 there is just one variable related to DOT, indicating DOT was effectively conducted in this case.

Tuberculosis direct cost analysis

The cost per reported case of sensitive active pulmonary TB was calculated considering the sum of human resources, laboratory tests, and treatment medications as depicted above and in Supplementary Fig. S1: The cost was calculated taking in consideration the duration of the treatment reported in the SINAN and the year of the notification with the adjustment of the economic inflation[15] and the US dollar to Brazilian Real ratio fluctuations[16](Supplementary Table S3). We calculated the value per case according with the BrMrOH recommendations. The cost depicted is an assumption based in the guidelines provided from BrMOH. Examples and simulations are depicted in the Supplementary Tables S4 and S5.

- Human resources:
  - Doctor/physician base salary consult value provided from the Ministry of Health, were utilized and corrected per inflation values yearly. One

Characteristics	New Case	Retreatment	p-value
	N = 345,908	N = 80,132	
Age (IQR)	40.9 (16.4)	40.1 (14.2)	<0.0001
Race			<0.0001
White	101,548 (29.4%)	19,891 (24.8%)	
Non-white	219,494 (63.5%)	53,711 (67.0%)	
Missing	24,866 (7.19%)	6530 (8.15%)	
Sex			<0.0001
Female	101,525 (29.4%)	18,162 (22.7%)	
Male	244,353 (70.6%)	61,964 (77.3%)	
Missing	30 (0.01%)	6 (0.01%)	
Schooling (years)			<0.0001
<5	38,504 (11.1%)	10,454 (13.0%)	
≥5 to <9	81,719 (23.6%)	23,297 (29.1%)	
≥9 to<12	99,519 (28.8%)	19,139 (23.9%)	
≥12	20,806 (6.01%)	2040 (2.55%)	
Missing	105,360 (30.5%)	25,202 (31.5%)	
HIV infection	22,318 (6.45%)	101,74 (12.7%)	<0.0001
'Missing'	52,035 (15.0%)	12,177 (15.2%)	
Alcohol use	61,676 (17.8%)	22,848 (28.5%)	<0.0001
'Missing'	19,832 (5.73%)	5059 (6.31%)	
Diabetes	31,962 (9.24%)	4780 (5.97%)	<0.0001
'Missing'	19,832 (5.73%)	5059 (6.31%)	
Mental illness	7684 (2.22%)	2387 (2.98%)	<0.0001
'Missing'	20,922 (6.05%)	5293 (6.61%)	
Smoking	85,085 (24.6%)	26,109 (32.6%)	<0.0001
'Missing'	21,706 (6.28%)	5386 (6.72%)	
Smear grade			<0.0001
Negative	52,440 (15.2%)	14,883 (18.6%)	
Positive	203,987 (59.0%)	45,716 (57.1%)	
Not performed	82,748 (23.9%)	17,897 (22.3%)	
'Missing'	6733 (1.95%)	1636 (2.04%)	
Abnormal Chest X-ray	247,406 (71.5%)	53,781 (67.1%)	<0.0001
'Missing'	90,410 (26.1%)	24,853 (31.0%)	
Smear culture			<0.0001
Negative	30,624 (8.85%)	10,918 (13.6%)	
Not performed	221,152 (63.9%)	43,365 (54.1%)	
Positive	88,134 (25.5%)	24,231 (30.2%)	
'Missing'	5998 (1.73%)	1618 (2.02%)	
TB drug resistance			<0.0001
Sensitive	48,769 (14.1%)	14,718 (18.4%)	
Resistant to Isoniazid	564 (0.16%)	223 (0.28%)	
Resistant to Isoniazid and Rifampicin	103 (0.03%)	75 (0.09%)	
Resistant to other first-line drugs	852 (0.25%)	327 (0.41%)	
Resistant to Rifampicin	194 (0.06%)	89 (0.11%)	
On going	4400 (1.27%)	1472 (1.84%)	
Not performed	128,608 (37.2%)	24,568 (30.7%)	
Missing	162,418 (47.0%)	38,660 (45.92%)	
Directly observed therapy	135,750 (39.2%)	26,949 (48.2%)	<0.0001
Treatment outcomes			<0.0001
Cure	283,905 (82.1%)	50,271 (62.7%)	
Death	13,691 (3.96%)	3818 (4.76%)	
Failure	266 (0.08%)	117 (0.15%)	
LTFU	48,046 (13.9%)	25,926 (32.4%)	

(Table 1 continues on next page)

Characteristics	New Case	Retreatment	p-value
	N = 345,908	N = 80,132	
(Continued from previous page)			
Molecular test			<0.0001
Sensible to Rifampicin	108,591 (31.4%)	26,252 (32.8%)	
Resistant to Rifampicin	1615 (0.47%)	572 (0.71%)	
Inconclusive	5022 (1.45%)	1108 (1.38%)	
Not Detectable	13,615 (3.94%)	4496 (5.61%)	
Not performed	187,348 (54.2%)	39,946 (49.9%)	
Missing	29,717 (8.59%)	7758 (9.68%)	

Data represent no. (%), except for age, which is presented as median and interquartile range (IQR). *Definition of alcohol use:* Past or current any consumption of alcohol. *Definition of smoking:* Past or current smoking of tobacco. *Definition of non-white race:* combination of black, mixed, *pardo*, yellow and indigenous. *Definition of drug use:* Past or current drug use (marijuana, cocaine, heroin, or crack). TB: tuberculosis; LTFU: loss to follow-up.

Table 1: **Characteristics of Brazilian pulmonary tuberculosis cases notified between 2015 and 2022, according to history of anti-tuberculosis treatment.**

monthly consultation was considered for patients undergoing treatment.[17]

- Community health agent: In patients who underwent DOT, the Ministry of Health recommends a minimum of 3 (three) doses of medication supervised by community health agents during home visits, representing 3 (three) weekly visits per month of treatment. The value of each visit was calculated according to the base salary given by the federal government, that is calculated representing 2 (two) times the minimum salary in the country.[18] This salary was updated per year of the study. Considering the number of monthly visits made and the average duration of visits the cost of each visit was calculated.[19]

- Laboratory tests: the values obtained through the cost table of the Brazilian Unified Health System were considered.[20] For the molecular test that is not included in this table, the value previously reported[21] was used as a reference. We corrected the values according with the inflation yearly.[15]
  - Sputum smear microscopy was considered in each month of treatment.
  - Sputum culture and sensitivity test were considered as an accomplishment at the time of diagnosis.
  - Molecular test: Considered to be conducted at the time of diagnosis.
- Treatment cost: To perform this calculation, the National Health Surveillance Agency (ANVISA) table was used, which predicts the value of each treatment pill paid for by the government.[22] The weight of each adult patient between 51 and 70 kg was used as a reference. We adjusted the treatment cost according with the economy inflation. The cost of the treatment was divided into an intensive phase and a maintenance phase[10]:
  - Intensive Phase: used as a basis for the combined medicine 4 in 1 (rifampicin + isoniazid + ethambutol + pyrazinamide), consumed 04 pills a day during the first two months.
  - Maintenance Phase: We considered using the 2:1 drug (rifampicin + isoniazid), using two pills a day.

Overall, the cost calculated takes into account the duration of the individual's permanence in the notification system, which influences the number of medication pills used and the number of tests and consultations performed. After calculating the cost per case, we summed the value of each case for each year of the study.

Number Needed to treat analysis

To determine the NNT of the DOT, in each study subpopulation considering the anti-TB treatment outcomes we calculated the Absolute Risk Reduction (ARR) first (Experimental Event Rate (EER) from the Control Event Rate (CER): $ARR = CER - EER$). The NNT is obtained by taking the inverse of the ARR ($NNT = 1/\text{ARR}$).[23]

Statistical analysis

Clinical and epidemiologic variables were presented as frequency and percentage (%) for categorical data, while continuous variables were expressed as the median and interquartile range (IQR). Descriptive analyses were employed to provide an overview of the distribution and key characteristics of the following: (I) the overall study population, as well as subgroups such as (II) Retreatment and New cases, and (III) Vulnerable populations. Additionally, we stratified costs by vulnerability, year, and prior TB history. To evaluate estimate the probability of cure relative to the dollar amount invested per pulmonary TB case we fit a Bayesian multivariate linear model using the following variables: (i) cost; (ii) sex; (iii) history of anti-TB treatment; and (iv) vulnerability factors, including homelessness, incarceration, drug use, healthcare work, living with HIV, pregnancy, and

Characteristics	Non-vulnerable	Vulnerable	p-value
	N = 282,190	N = 109,940	
Age (IQR)	43.9 (17.0%)	34.7 (11.7%)	<0.0001
Race			
White	82,384 (29.2%)	29,949 (27.2%)	<0.0001
Non-white	180,152 (63.8%)	70,411 (64.0%)	
Missing	19,654 (6.96%)	9580 (8.71%)	
Sex			
Female	96,768 (34.3%)	18,184 (16.5%)	<0.0001
Male	185,396 (65.7%)	91,748 (83.5%)	
Missing	26 (0.01%)	8 (0.01%)	
Schooling (years)			
<5	34,925 (12.4%)	10,243 (9.32%)	<0.0001
≥5 to <9	61,079 (21.6%)	32,135 (29.2%)	
≥9 to<12	81,690 (28.9%)	29,283 (26.6%)	
≥12	17,272 (6.12%)	4945 (4.50%)	
Missing	87,224 (30.9%)	33,334 (30.3%)	
Alcohol use	40,719 (14.4%)	28,095 (25.6%)	<0.0001
Missing	14,602 (5.17%)	8086 (7.35%)	
Diabetes	32,403 (11.5%)	3627 (3.30%)	<0.0001
Missing	15,087 (5.35%)	8229 (7.48%)	
Mental illness	6205 (2.20%)	2602 (2.37%)	<0.0001
Missing	16,108 (5.71%)	8412 (7.65%)	
Smoking	54,810 (19.4%)	36,321 (33.0%)	<0.0001
Missing	17,434 (6.18%)	8502 (7.73%)	
Smear grade			<0.0001
Negative	45,189 (16.0%)	16,775 (15.3%)	
Not performed	63,044 (22.3%)	28,565 (26.0%)	
Positive	168,318 (59.6%)	62,452 (56.8%)	
Missing	5639 (2.00%)	2148 (1.95%)	
Abnormal Chest X-ray	213,752 (75.7%)	68,099 (61.9%)	<0.0001
Missing	61,562 (21.8%)	39,715 (36.1%)	
Smear culture			<0.0001
Negative	26,621 (9.43%)	11,183 (10.2%)	
Not performed	186,733 (66.2%)	60,859 (55.4%)	
Positive	64,041 (22.7%)	35,855 (32.6%)	
Missing	4795 (1.70%)	2043 (1.86%)	
TB drug resistance			<0.0001
Sensitive	31,628 (11.2%)	23,458 (21.3%)	
Resistant to Isoniazid	423 (0.15%)	261 (0.24%)	
Resistant to Isoniazid and Rifampicin	95 (0.03%)	56 (0.05%)	
Resistant to other first-line drugs	709 (0.25%)	321 (0.29%)	
Resistant to Rifampicin	162 (0.06%)	83 (0.08%)	
On going	3554 (1.26%)	1596 (1.45%)	
Not performed	104,437 (37.0%)	38,472 (35.0%)	
Missing	141,182 (50.03%)	45,693 (41.6%)	
Directly observed therapy	105,175 (37.3%)	43,278 (39.4%)	<0.0001
Molecular test			
Sensible to Rifampicin	78,829 (27.9%)	41,126 (37.4%)	
Resistant to Rifampicin	1369 (0.49%)	571 (0.52%)	<0.0001
Inconclusive	4333 (1.54%)	1372 (1.25%)	
Not Detectable	11,436 (4.05%)	4985 (4.53%)	
Not performed	159,307 (56.5%)	53,035 (48.2%)	
Missing	26,916 (9.54%)	8851 (8.05%)	

(Table 2 continues on next page)

Characteristics	Non-vulnerable	Vulnerable	p-value
	N = 282,190	N = 109,940	
(Continued from previous page)			
Treatment outcomes			
Cure	233,007 (82.6%)	79,542 (72.4%)	<0.0001
Death	11,681 (4.14%)	4225 (3.84%)	
Failure	292 (0.10%)	70 (0.06%)	
LTFU	37,210 (13.2%)	26,103 (23.7%)	

Data represent no. (%), except for age, which is presented as median and interquartile range (IQR). *Definition of alcohol use:* Past or current any consumption of alcohol. *Definition of smoking:* Past or current smoking of tobacco. *Definition of non-white race:* combination of black, mixed, *pardo*, yellow and indigenous. *Definition of drug use:* Past or current drug use (marijuana, cocaine, heroin, or crack). TB: tuberculosis; LTFU: loss to follow-up.

Table 2: **Characteristics of Brazilian pulmonary tuberculosis cases notified between 2015 and 2022, according to vulnerability status.**

migration and (v) year. In this case our model could be denoted as:

$$y \sim Bernoulli(p)$$

$$\log\left[\frac{P(cure=1)}{1-P(cure=1)}\right] = \beta_i * X_i$$

where: i is the ith row of the model matrix; β is a vector of unknown parameters and X_i is the ith variable used as a predictor what is our case means (i) cost; (ii) sex; (iii) previous TB, (iv) vulnerability and (v) year. Note that in this case cost and year area numerical variable while the other ones are categorical so our fully model could be expressed as:

$$\beta_0 + \beta_1 * Cost + \beta_2 * Sex_{male=1} + \beta_3 * PT_{yes=1} +$$

$$\sum_p^n \beta_p * PopVul_p + \beta_{12} * Year$$

It's important to point that in vulnerability a total of seven parameters where estimated, one for each population (i.e., drug user, persons with HIV, homelessness, immigrants, liberty depravation, pregnant and health worker). For each of the priors associated with a term (i.e., variable in model) was assigned a flat prior based on Uniform (-inf,inf). Cases reported as cured with less than 30 days of stay in the system (time between the date of notification and closure of the case) were excluded from the cost model. The model has at least two important proprieties. First, we could derivate the aOR associated with each variable just by take the exp(β) and the increase probability associated with 1 unit change by taking 1/(1-exp (-β)). Parameters estimation was conducting using No-U-Turn (NUTS) sampler in the R brms package (i.e., a Stan wrapper). A total of 4 chains were running with 2000 iterations sample per chains. The first 1000 cycles were used as burn-in period. Model convergence and adequability were accessed using trace plot and Rhat (i.e., check chain convergence), and posterior predictive check (i.e., sample data from model and compare with model observed) (Supplementary Fig. S2). All analyses were conducted using R 4.2.1, and the corresponding code has been made available at https://github.com/rodriguesmsb/neapTB for transparency and reproducibility.

Ethics statement

All data analysed in this study were obtained from a public government program (SINAN-TB) and were pre-processed by the Brazilian Ministry of Health (https://datasus.saude.gov.br/informacoes-de-saude-tabnet/). The datasets were verified by eliminating duplicate registrations and ensuring consistency and completeness of registered data, following the regulations dictated by Resolution No. 466/12 on Research Ethics of the National Health Council, Brazil. This study did not require written informed consent for participation under national legislation and institutional requirements.

Role of the funding source

The funding source had no role in study design, data collection, analysis and interpretation, or the decision to submit the work for publication.

Results

Characteristics of the study participants

Between 2015 and 2022, Brazil reported a total of 743,823 TB cases. We specifically focused on cases with pulmonary TB, resulting in a subset of 630,950 cases. To refine our analysis, we excluded 30,417 cases involving children (<18 years), 4529 TB cases diagnosed post-mortem, and 132,245 lacking information on treatment initiation and completion. Also, 5462 were excluded due be reported as cure but just have less than 30 days of treatment reported in the system. This exclusion was necessary as it made calculating medicine costs per day unfeasible. It is important to highlight the exclusion of an additional 1644 cases due to missing outcome data, 4205 of diagnosis change, 20,481 cases transferred to another healthcare unit, and 5927 cases

due to treatment modifications. Following these exclusions, our study comprised a total of 426,040 pulmonary TB cases. These cases were further stratified based on social vulnerabilities and previous anti-TB treatment history for a more refined analysis (Fig. 1).

Characteristics of the overall study population are shown in Supplementary Table S2. The majority of the study population was male, with a median age of 41.2 years. Non-white self-reported race was more prevalent (64.1%), and a significant proportion had attained a moderate level of formal schooling (24.6% –5 to 9 years; 27.9% 9–12 years). The overall population exhibited 58.6% smear grade positive result, with a substantial number of cases reporting either not performed or missing information (Not performed:23.6%). A similar trend was observed for drug resistance tests (Not performed:36.0%, Missing:47.2%), molecular tests (Not performed: 53.4%), smear culture (Not performed: 62.1%), and chest X-ray (Missing: 27.1%). The utilization of DOT was lower than expected, covering only 38.2% of the population. Regarding substance consumption habits, 19.8% reported alcohol use, while 26.1% reported tobacco use. The characteristics among the subpopulations stratified according to previous anti-TB treatment history and social vulnerabilities were depicted in Tables 1 and 2, respectively.

Evaluating the direct cost of pulmonary TB from 2015 to 2022

The overall cost of pulmonary TB treatment in Brazil exhibited variations over the years, reaching its highest value in 2017 (21.38 million dollars) and the lowest in 2022 (9.98 million dollars), accumulating to a total cost of 108 million dollars spent over the 7-year period (Fig. 2a). Further stratifying the cost based on the history of anti-TB treatment, surprisingly, despite fluctuations in the total cost and the cost of new cases, the cost of retreatment cases remained stable over the years with an accumulated total of 23,5.million dollars (Fig. 2b). Subsequently, we assessed the cost per social vulnerability, revealing that in the accumulated cost people deprived of liberty, people who use drugs, and people living with HIV emerged as the top three in terms of cost, respectively (Fig. 2d).

Impact of directly observed treatment and potential target subpopulations

To assess the impact of DOT on treatment outcomes, we conducted a comparative analysis of anti-TB treatment outcome rates across the entire study population and further stratified within subpopulations. First, we identified the covered DOT among the overall study population (Supplementary Fig. S3) and tested each subpopulation (Supplementary Fig. S4). To identify a target population for the implementation of DOT, we calculated the NNT, representing the number of patients needed to undergo the intervention for one of them to experience an expected effect. For the overall population, the NNT was determined to be 6.81 (Fig. 3). Upon stratifying this group based on the history of anti-TB treatment, new cases exhibited an NNT of 8.15, while retreatment cases demonstrated an NNT of 4.56 (Fig. 4). Further stratification according to the presence of social vulnerabilities revealed that the homeless group (NNT: 3.0), people who use drugs (NNT: 3.72), and immigrants (NNT: 5.66) displayed the most effective response to DOT. People living with HIV (NNT: 6.36) and people deprived of liberty (NNT: 6.86) exhibited a response pattern similar to the general population (Fig. 5). Conversely, healthcare workers and pregnant women presented higher NNT values than the overall study population, indicating a relatively lower cost-effectiveness of DOT in these subgroups. Noteworthy that we recognize the significance of DOT as a substantial factor influencing the cost per treated TB case (Supplementary Table S4). Importantly, introducing DOT across all groups resulted in improved cure rates and a significant reduction in LTFU and deaths.

Economic investment required to achieve the world health organization treatment success targets for end tuberculosis

We conducted an economic analysis to determine the investment required to achieve the WHO-recommended 90% treatment success rate. By employing a multivariate generalized linear model, we estimated the probability of cure per dollar invested, considering cure as a successful outcome, and combining death and LTFU as unfavourable outcomes. Initially, an investment of $ 275 was identified as necessary for the overall population to achieve a 90% cure rate. Further delineating the groups based on treatment history, the new case subgroup required a similar investment of $276 to attain the 90% cure rate, mirroring the overall population. However, the retreatment group necessitated increased efforts, with an investment of $318 for the same target (Fig. 6).

We further stratified the overall population based on social vulnerabilities. Comparing vulnerable and non-vulnerable populations initially revealed a distinct investment requirement ($ 307 vs. $275, respectively), with a similar pattern observed when considering treatment history (entry mode). Subsequently, we delved into each vulnerability group, finding that healthcare workers required the least economic investment, at $217, to achieve a 90% cure rate. Notably, even without any investment, this group already exhibited a probability of cure surpassing 50%.

As expected, the homeless group demanded more substantial efforts, with an initial probability of cure close to zero without investment and a requirement of $366 to achieve the expected probability of cure. This was followed by people who use drugs ($341), people living with HIV ($297), pregnant women ($294) and immigrants ($287). Another significant observation was

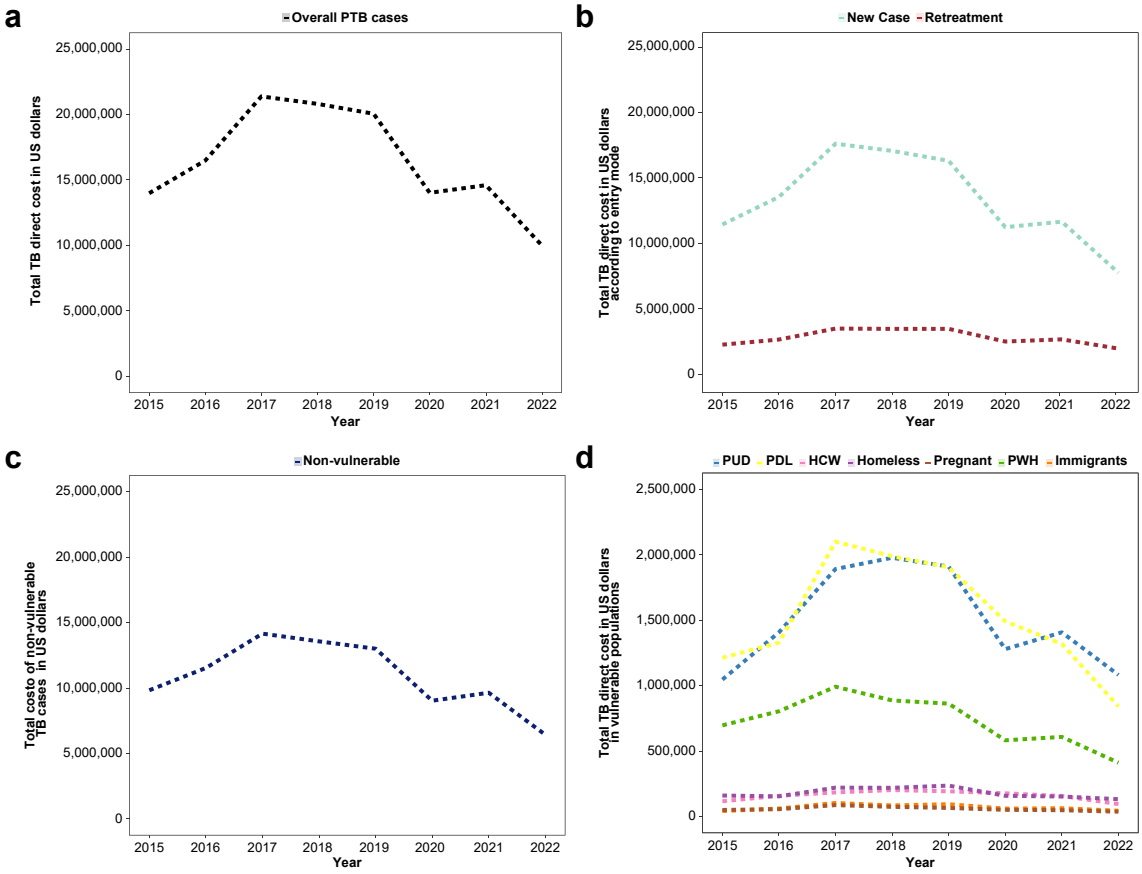

***Fig. 2:* Overview of the total cost of PTB in Brazil between 2015 and 2022.** (a) The total cost of PTB in Brazil shows the cumulative economic burden over the seven years. (b) Cost based on the history of ATT, distinguishing between new cases and retreatment cases. (c–d) Cost analysis according to social vulnerability. The cost per case was calculated considering the duration from the start to the completion or abandonment of treatment. Abbreviations: TB: tuberculosis; people who use drugs: People who use drugs; PDL: People deprived of liberty; HCW: Health Care Workers.

that persons deprived of liberty demonstrated better cure rates without investment than the non-vulnerable group, achieving a 90% probability with an investment of $263 (Fig. 7).

Our final analysis examined the intersection of treatment history and social vulnerabilities (Supplementary Fig. S5) to investigate potential influences on the required economic investment. Our findings revealed that the history of treatment accentuated the existing disparities in economic efforts, as highlighted in our previous analysis of social vulnerabilities (Fig. 8 and Supplementary Fig. S6).

Discussion

The economic burden of pulmonary TB is remarkably high, especially in LMICs such as Brazil. Our study represents a significant milestone as the first national attempt to quantify the direct cost of pulmonary TB to the healthcare system. By conducting this study, we have addressed a crucial knowledge gap, shedding light on populations that are more cost-effective for implementing DOT and estimating the investment needed to achieve the treatment success goals outlined by the WHO. The study underscores the importance of implementing DOT and tailoring its application to vulnerable populations and/or the history of anti-TB treatment.

The total TB cost to the public health system over the last seven years amounted to approximately $1.3 billion. While costs varied according to each population, attention is drawn to the expenditure on retreatment cases, totalling $23.5 million. It is important to note that this figure does not account for the cost of the first treatment for each patient. Also, a huge part of the retreatment cases presented LTFU as the anti-TB treatment outcome, potentially representing a great barrier to the sustainability of the healthcare system.

The calculated direct cost per pulmonary TB case is influenced by various factors, with DOT, as recommended by the Brazilian Ministry of Health,[7] being an

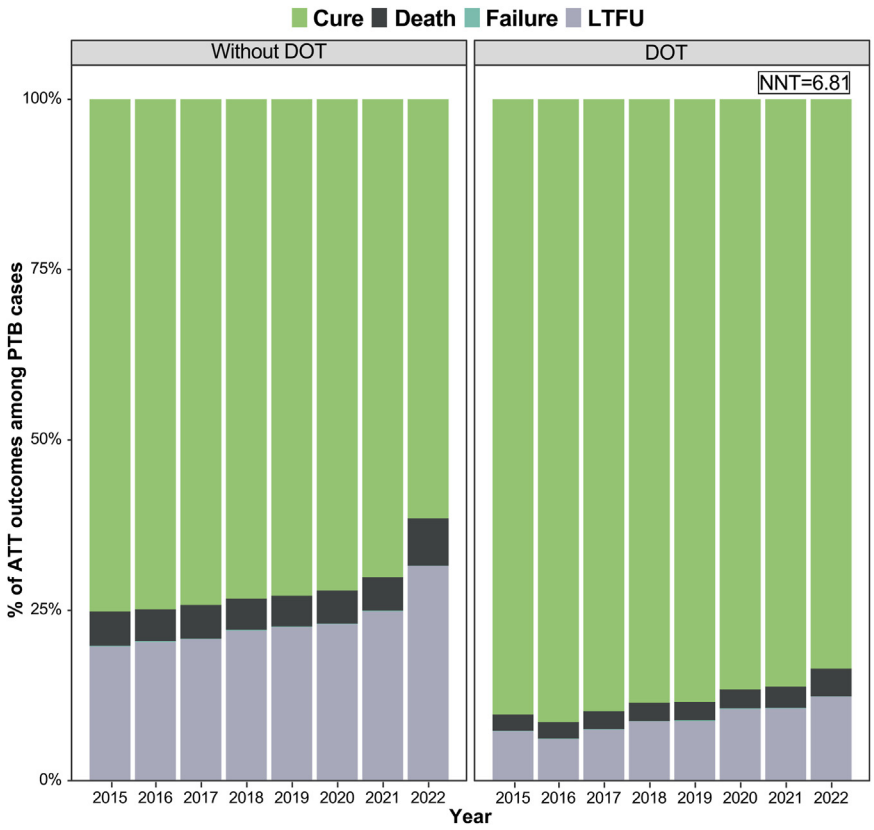

Fig. 3: **Bar plot depicts the impact of DOT implementation on ATT outcomes among the overall study population between 2015 and 2022.** Abbreviations: DOT: Direct Observed treatment; ATT: anti-tuberculosis treatment; PTB: pulmonary tuberculosis.

important contributor. When implemented in person by a healthcare professional at least three times a week, DOT constitutes a crucial factor, accounting for almost a third of the total cost per patient. It is essential to highlight that alternative DOT modalities, beyond in-person supervision, have been successfully implemented in other countries,[24,25] offering an opportunity to diversify approaches and reduce costs. Focusing

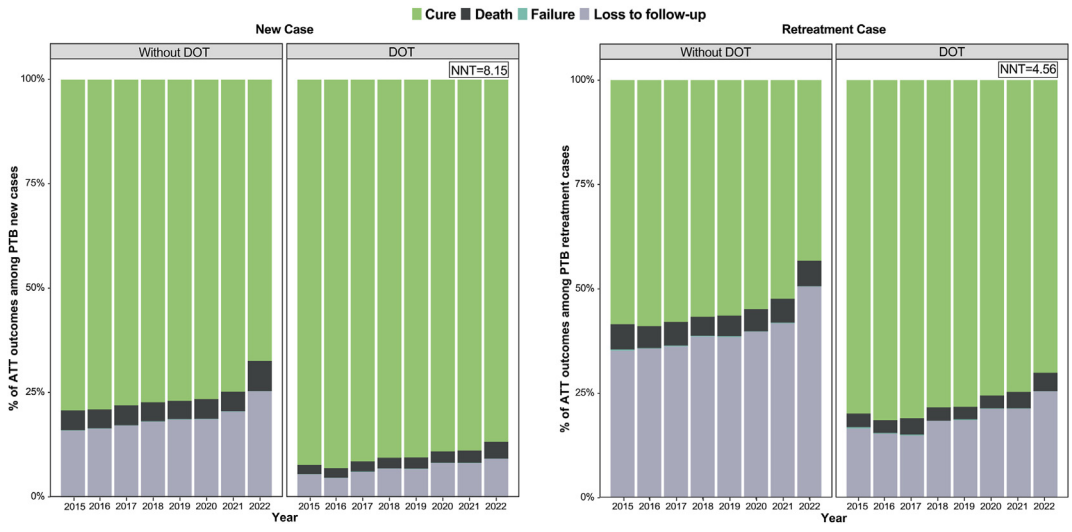

Fig. 4: **Bar plot depicts the impact of DOT implementation on ATT outcomes among PTB cases according to the history of ATT between 2015 and 2022.** Abbreviations: DOT: Direct Observed treatment; ATT: anti-tuberculosis treatment; PTB: pulmonary tuberculosis.

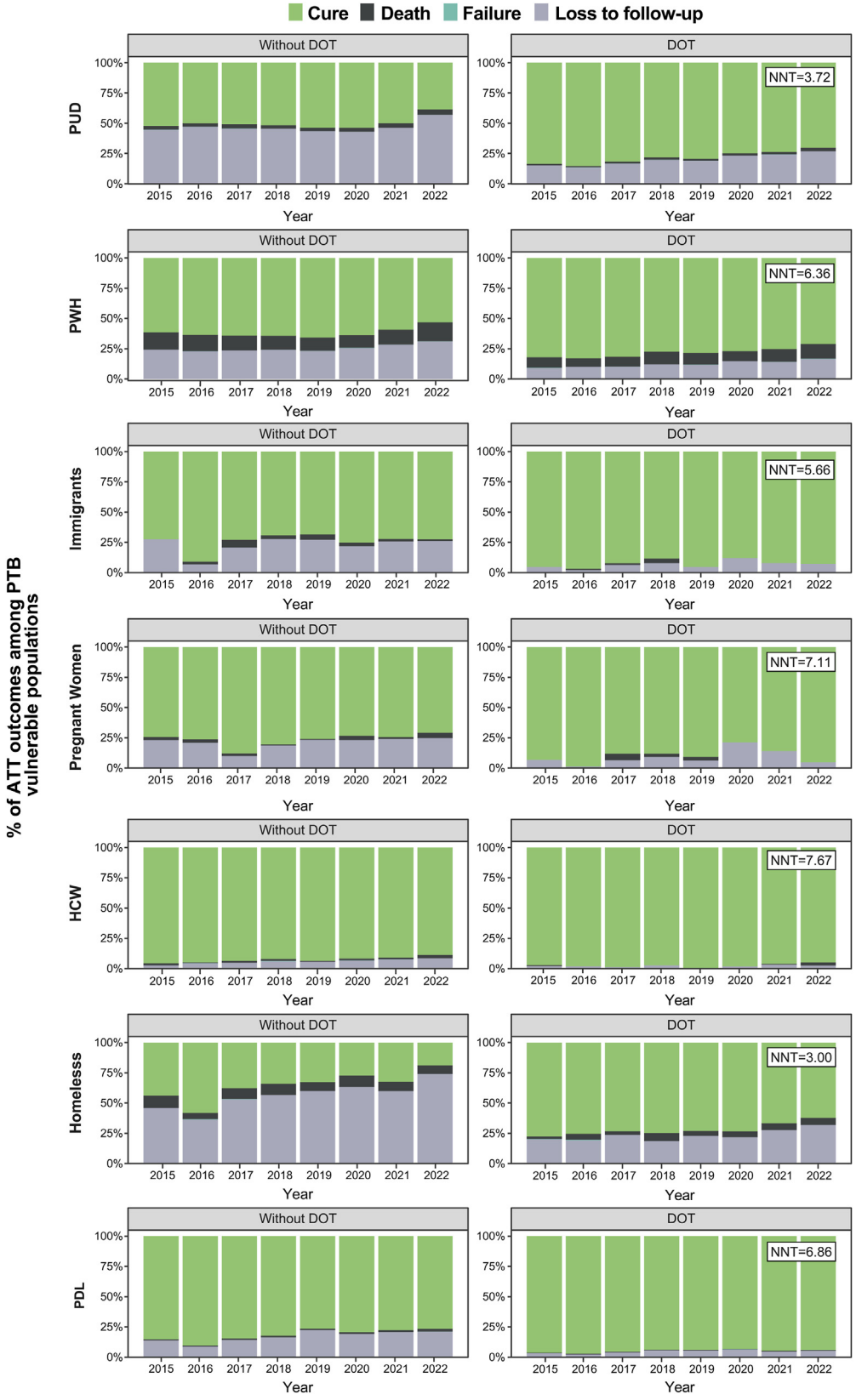

Fig. 5: **Bar plot depicts the impact of DOT implementation on ATT outcomes among PTB cases according to the social vulnerability between 2015 and 2022.** Abbreviations: DOT: Direct Observed treatment; ATT: anti-tuberculosis treatment; PTB: pulmonary tuberculosis.

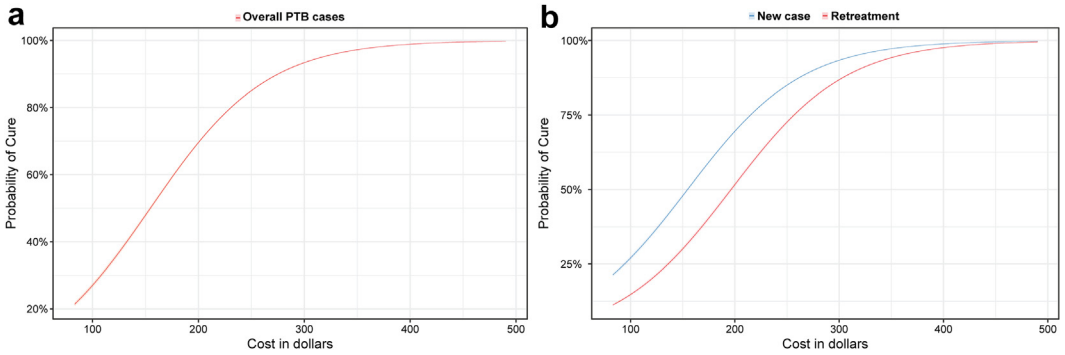

Fig. 6: **Binomial regression models illustrating the cost per case to increase the probability of cure during ATT.** (a) Depicts the cost per case in the overall PTB cases. (b) Represents the cost per case based on the history of ATT. (c) Illustrates the cost per case based on the presence or absence of social vulnerabilities. (d) Stratifies the cost per case based on each social vulnerability in the study. Abbreviations: PTB: Pulmonary Tuberculosis; ATT: Anti-Tuberculosis Treatment; PUD: People who use drugs; PDL: People deprived of liberty; HCW: Health Care Worker.

in-person strategies on groups at higher risk of treatment non-adherence and employing online or telephonic modalities for groups at lower risk of follow-up loss could enhance TB management's cost-effectiveness.

As expected, the reduction in reported cases during the pandemic translated into a reduction in the economic burden of pulmonary TB in 2022.[1,26] However, a return to pre-pandemic spending levels is expected, given the substantial number of undiagnosed cases that are anticipated to enter the healthcare system. Intriguingly, both the cost and the number of notifications for retreatment cases remain constant, despite a significant decline in all other groups, proportionate to the overall reduction in the country's notifications. This emphasizes the need to identify this group at the first point of care and provide more individualized treatment. Additionally, for cases already identified as retreatment, previous studies have shown a higher propensity for them to lose follow-up again, likely resulting in a new cycle of retreatment and increased transmission of primary drug resistant TB in the community.[27]

Our results highlight the positive impact of DOT on TB treatment outcomes, particularly in specific populations such as retreatment cases and those with social vulnerabilities like individuals experiencing homelessness and people who use drugs. Interestingly, these populations also exhibited lower DOT coverage. In Brazil, DOT is a public policy with equal coverage for all TB patients, predominantly offered through basic health units, even for retreatment cases or in the presence of social vulnerabilities without target coverage to this specific population.[10] Only patients resistant to one of the first-line drugs are referred for more individualized care at secondary healthcare units which may represent a barrier to achieving higher rates of successful anti-TB treatment outcomes.

Consistent with our prior studies, social vulnerability and retreatment are risk factors for unfavourable TB treatment outcomes in Brazil.[9,28] This aligns with our

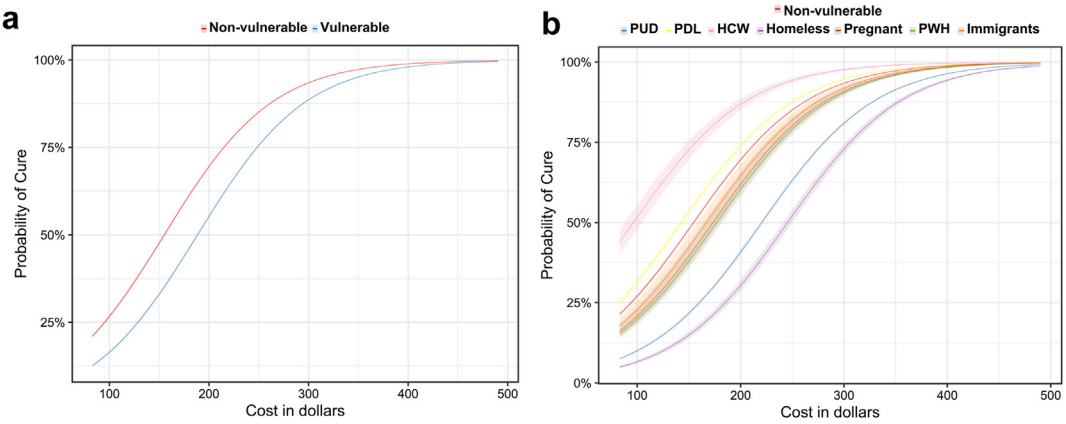

Fig. 7: **Binomial regression models depict the cost per case to increase the probability of cure during ATT among vulnerable and non-vulnerable subgroups.** Abbreviations: ATT: anti-tuberculosis treatment; PUD: People who use drugs; PDL: People deprived of liberty; HCW: Health Care Worker.

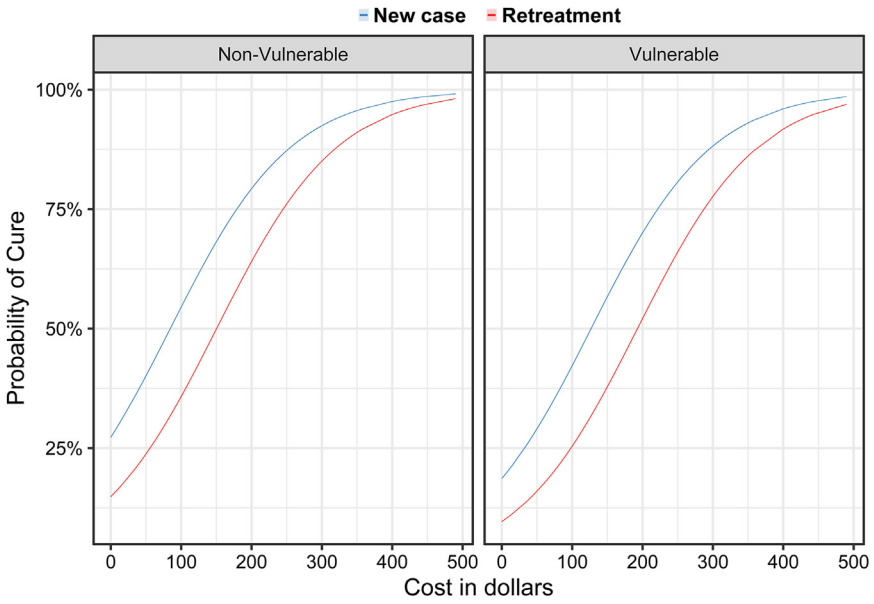

Fig. 8: **Binomial regression models depict the cost per case to increase the probability of cure during ATT among vulnerable and non-vulnerable subgroups stratified according to the ATT history.** Abbreviations: ATT: anti-tuberculosis treatment.

findings, from the presentation of clinical characteristics of patients to the high number of patients without microbiological tests such as drug sensitivity tests and molecular tests. This fact poses a significant public health problem, as they hinder the detection of drug-resistant strains, creating challenges for both patient progression and community health due to the risk of resistant strain dissemination.

Subpopulations with lower NNT also incurred more significant costs to achieve WHO targets. For example, people experiencing homelessness and those who use drugs cost an additional $91 and $66 per TB case, respectively, compared to the general population. These findings corroborate the literature,[2] emphasizing that more vulnerable populations are harder to reach, becoming a public health challenge. Notably, when overlaying risk factors such as treatment history and social vulnerability, achieving high cure rates becomes even more challenging without substantial economic investment.[29] Here, we highlight vulnerable and retreatment populations as specific targets for DOT implementation.

Our study has limitations. The retrospective nature of our investigation relies heavily on the available data in the SINAN-TB, which may be subject to reporting biases and incomplete records. We excluded cases without information about treatment implementation, completion, or interruption. Due to the lack of data on patient weight, we had to exclude children and adolescents, whose treatment regimens differ significantly from the adult population and are heavily influenced by weight. Additionally, the absence of systematic reporting on DOT visits by healthcare community workers, the number of missed doses, physician consultations, and the significant amount of missing data on tests performed led us to make calculations based on assumptions using the cascade of care recommended by the Brazilian Ministry of Health and may not reflect the true burden of TB. Because the number of cases reported as treatment failures is substantially smaller than those for other unfavourable outcomes (LTFU and death), it was not possible to include this group in the cost model. Future studies need to address these important subpopulations. The economic analysis primarily focuses on direct healthcare costs related to pulmonary TB, omitting costs related to hospitalization, maintenance of health unit infrastructure, indirect costs such as productivity loss, undiagnosed cases, death, patient expenses, and the broader societal impact.

Despite these limitations, our study provides insights into the economic aspects of pulmonary TB in Brazil and highlights the effectiveness of DOT across various patient groups, regardless of their vulnerabilities or previous anti-TB treatment history. It also identifies key subpopulations, such as homeless individuals and people who use drugs, as possible targets for resource allocation strategies in TB control programs.

Contributors

Conceptualization, B.B-D., M.M.R and B.B.A.; Data verification and curation, B.B-D., M.M.R, KV-S., V.M.S.C., M.A-P., and B.B.A.; Investigation, B.B-D, M.M.R, and B.B.A.; Formal analysis, B.B-D., M.M.R., and B.B.A.; Funding acquisition, M.M.R., and B.B.A.; Methodology, B.B-D., M.M.R., and B.B.A.; Project administration, B.B-D, B.B.A.; Resources, B.B.-D., A.L.K., and B.B.A.; Software, B.B-D., M.M.R, M.A-P., and

B.B.A.; Supervision, M.M.R., M.C–S., and B.B.A.; Writing—original draft, B.B-D., M.M.R., K.V–S., and B.B.A.; Writing—review and editing, all authors. All authors had full access to all the data in the study and B.B.A. was responsible for the decision to submit the manuscript.

Data sharing statement

The data and codes that support the findings of this study are available at https://github.com/rodriguesmsb/neapTB.

Declaration of interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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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.2024.100905.

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