Interplay between biological & social vulnerability and poor tuberculosis treatment outcome in Brazil: a nationwide study using multivariate modelling with excess risk

Beatriz Barreto-Duarte,[a,b,c,d,e,**,s] Klauss Villalva-Serra,[a,c,s] João P. Miguez-Pinto,[a,c] Mariana Araújo-Pereira,[c,d,e] Vanessa M. S. Campos,[a,c] Isabella B. B. Ferreira,[c,f] Betânia M. F. Nogueira,[c,d,g] Artur T. L. Queiroz,[c,h] Valeria C. Rolla,[i] Marcelo Cordeiro-Santos,[j,k,l] Afrânio L. Kritski,[b,m] Leonardo Martinez,[n] Peter F. Rebeiro,[o] Timothy R. Sterling,[o] Moreno M. Rodrigues,[c,p,t] and Bruno B. Andrade[a,b,c,d,e,f,g,q,r,*,t]

[a]Curso de Medicina, Universidade Salvador (UNIFACS), Salvador, Brazil
[b]Programa Pós-graduação de Clínica Médica. Faculdade de Medicina, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil
[c]Multinational Organization Network Sponsoring Translational and Epidemiological Research (MONSTER) Initiative, Salvador, Brazil
[d]Instituto de Pesquisa Clínica e Translacional, Faculdade Zarns, Clariens Educação, Salvador, Brazil
[e]Laboratório de Pesquisa Clínica e Translacional, Instituto Gonçalo Moniz, Fundação Oswaldo Cruz, Salvador, Brazil
[f]Programa de Pós-Graduação em Medicina e Saúde Humana, Escola Bahiana de Medicina e Saúde Pública (EBMSP), Salvador, Brazil
[g]Programa de Pós-Graduação em Ciências da Saúde, Universidade Federal da Bahia, Salvador, Brazil
[h]Center of Data and Knowledge Integration for Health, Instituto Gonçalo Moniz, Fundação Oswaldo Cruz, Salvador, Brazil
[i]Instituto Nacional de Infectologia Evandro Chagas, Fundação Oswaldo Cruz, Rio de Janeiro, Brazil
[j]Fundação Medicina Tropical Doutor Heitor Vieira Dourado, Manaus, Brazil
[k]Programa de Pós-Graduação em Medicina Tropical, Universidade do Estado do Amazonas, Manaus, Brazil
[l]Faculdade de Medicina, Universidade Nilton Lins, Manaus, Brazil
[m]Programa Acadêmico de Tuberculose da Faculdade de Medicina, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil
[n]Department of Epidemiology, School of Public Health, Boston University, Boston, MA, USA
[o]Division of Infectious Diseases, Department of Medicine, Vanderbilt University School of Medicine, Nashville, TN, USA
[p]Laboratório de Análise e Visualização de Dados, Fundação Oswaldo Cruz, Porto Velho, Brazil
[q]Department of International Health, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, USA
[r]Division of Infectious Diseases, Department of Medicine, Johns Hopkins University, Baltimore, MD, USA

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Summary

Background Focusing on socially vulnerable sub-populations at increased risk of tuberculosis is warranted to decrease the disease burden. In this study, we evaluated whether homelessness, living with HIV, incarceration, pregnancy, immigration, drug use, and healthcare work are inter-related risk factors for unfavorable anti-tuberculosis treatment (ATT) outcomes in Brazil through analysis of national disease registry database (SINAN).

Methods We conducted a retrospective cohort study of tuberculosis cases ≥18 years-old reported to SINAN between 2015 and 2023. Clinical and epidemiologic variables were compared between groups (non-vulnerability, homeless, people deprived of their liberty, pregnant women, people with HIV, people who use drugs, immigrants and healthcare worker). Bivariate comparisons identified characteristics associated with a composite unfavorable ATT outcome, or specifically death or LTFU versus cure. Multivariate modelling with relative excess risk due to interactions (RERI) were calculated to estimate how co-occurring vulnerabilities further increase the risk of unfavorable outcomes.

Findings Among 679,572 cases analysed, most were males aged 18–35 years-old, with non-white ethnicity. 16% of individuals without vulnerabilities experienced unfavourable outcomes, compared to 33% among those with at least one vulnerability. Overlapping vulnerabilities further amplified risk: for instance, unfavourable outcomes occurred in more than 67% of individuals who reported both homelessness and drug use. Interaction analyses revealed both synergistic and antagonistic effects, with the strongest additive synergy observed between HIV infection and drug use, with a RERI of 225% [174–304%].

*Corresponding author. Laboratório de Pesquisa Clínica e Translacional, Instituto Gonçalo Moniz, Fundação Oswaldo Cruz, Rua Waldemar Falcão, 121, Candeal, Salvador, Bahia,40296-710, Brazil.
**Corresponding author. Instituto de Pesquisa Clínica e Translacional, Faculdade ZARNS Salvador, Clariens Educação, Salvador, Brazil, CEP 41741-590.
E-mail addresses: bruno.andrade@fiocruz.br (B.B. Andrade), beatriz.duarte@monsterinitiative.com (B. Barreto-Duarte).
[s]These authors equally contributed to the work (co-first authors).
[t]These authors equally contributed to the work (co-senior authors).

Interpretation The superposition of interlacing social and biological vulnerabilities significantly worsened the risk of both death and LTFU in our population. Our study demonstrates that the joint effect of vulnerabilities on TB outcomes is not merely additive, but often synergistic, highlighting the importance of integrated and multisectoral interventions. These findings hallmark the need for policies that simultaneously address social and biological vulnerabilities to improve ATT success.

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Keywords: Tuberculosis; Vulnerable populations; Interactive effects; Epidemiology; Treatment outcome

Research in context

Evidence before this study

We used PubMed and Embase to search for publications, without language restriction, from the date of database inception to April 4th, 2025, that evaluated associations between vulnerable populations and tuberculosis (TB) outcomes in Brazil, using the terms "Tuberculosis" AND ("Vulnerable population" OR "Vulnerability" OR "Vulnerable") AND ("Unfavourable Treatment Outcome" OR "Treatment Outcome" OR "Loss to Follow Up" OR "Death") AND "Brazil". Our search returned 53 records. However, none of the retrieved studies examined the interactive effects of multiple co-occurring vulnerabilities, which is the central gap addressed by our analysis.

Added value of this study

Using nationally representative data from the Brazilian disease registry (Sistema de Informação de Agravos de Notificação, SINAN), we investigated 746,848 tuberculosis case notifications according to social (homelessness, incarceration, immigration, healthcare work, drug use, pregnancy, and previous ATT history/retreatment cases) and biological (living with HIV and tuberculosis-diabetes mellitus) in Brazil between 2015 and 2023. We identified the risk factors associated with unfavourable ATT outcomes (composite and individual outcomes: death or loss to follow up), highlighting the importance of the vulnerabilities such as homelessness, living with HIV, drug use, pregnancy, and immigration in affecting risk of unfavourable outcomes. To our knowledge, this is the first study in Brazil to systematically evaluate the interactive effects of co-occurring vulnerabilities using the Relative Excess Risk due to Interaction (RERI) framework, a methodological approach rarely applied in TB epidemiology. By quantifying how risks combine beyond their independent effects, our study contributes to the field of social epidemiology by moving from describing individual vulnerabilities to measuring how structural and biological risks intersect in real populations. We found that overlapping vulnerabilities, particularly between HIV infection and substance use (e.g., drugs and alcohol), substantially increased the risk of death and loss to follow-up beyond what would be expected from each condition alone. This study therefore provides important evidence on the relationship between social vulnerability, TB burden, and unfavourable ATT outcomes at the national level in Brazil, a country that has recently reinforced TB elimination as a priority. By applying interaction analysis to surveillance data, our findings advance methodological innovation in TB research and demonstrate how routine registries can be used to describe risk groups and to reveal the compounded effects of overlapping vulnerabilities. These insights could help inform both public health policies and clinical practices to improve ATT outcomes.

Implications of all the available evidence

Our findings have direct relevance for TB control policies in high-burden and inequitable settings. Recognizing the synergistic effects of overlapping vulnerabilities can guide more efficient resource allocation and tailored interventions. Practical strategies include strengthening directly observed therapy (DOT) coverage, ensuring continuity of care for individuals released from incarceration, and integrating TB programs with broader social protection measures (such as food support or housing initiatives). By explicitly addressing the intersection of social and biological determinants, health systems can design more effective, multisectoral responses to reduce TB-related inequities.

Introduction

Each year approximately 10 million people develop active tuberculosis (TB) worldwide and 1.3 million die from the disease.[1] The presentation of active TB is directly related to immunological status, degree of exposure to the pathogen, and the patient's socioeconomic conditions.[2,3] The presentation of active TB is directly related to immunological status, degree of exposure to the pathogen, and the patient's socioeconomic conditions.[2,3] Consequently, the burden of TB is disproportionately concentrated in populations with specific vulnerabilities. Without empirical research focused on these populations, it remains uncertain how their combined impact will influence progress toward

the End TB Strategy targets, which aim to reduce TB incidence by 80% and TB mortality by 90% by 2030.[4]

These vulnerabilities operate through both social and biological mechanisms. People deprived of liberty (PDL) face overcrowded and poorly ventilated conditions that facilitate transmission, while individuals experiencing homelessness encounter barriers to timely diagnosis and continuity of care, often compounded by substance use and comorbidities.[5–9] Immigrants may be affected by cultural, linguistic, and legal barriers that limit healthcare access, and people who use drugs are at increased risk of treatment interruption and immune dysfunction.[8] Similarly, alcohol and tobacco use have been consistently linked to higher risk of active TB and worse treatment outcomes, largely due to impaired immune function and reduced adherence to therapy.[10,11] On the biological side, people with HIV (PWH) have impaired immune responses that increase the likelihood of TB reactivation and poor outcomes, and those with diabetes mellitus show metabolic and immune alterations that heighten both disease severity and mortality risk.[12] Pregnant women, due to immunological and physiological changes, may present atypical clinical features that complicate early diagnosis and adherence to treatment, while healthcare workers remain at occupational risk of infection despite protective measures.[9,13–15] Finally, retreatment cases reflect prior therapeutic failure or relapse, conditions frequently associated with drug resistance and worse prognoses.

Brazil has one of the highest TB burdens worldwide.[16] The Brazilian Ministry of Health (BrMOH) has reported a concentrated epidemic of TB within vulnerable populations. Within this context, individuals experiencing homelessness face a 56-fold increased risk of developing active TB, whereas those with HIV and deprived of their liberty have a 28-fold higher risk compared to the general population.[17] Other populations, such as pregnant women, immigrants, and healthcare workers, are not systematically classified as vulnerable in national surveillance reports. As a result, risk estimates for these groups remain limited, although smaller studies suggest that they also face a disproportionate TB burden and worse ATT outcomes.

Despite the aforementioned observations, the burden of TB and the understanding of social vulnerabilities within the TB context remain underexplored, primarily due to the lack of precise census data characterizing vulnerable populations in Brazil. Additionally, the intricate relationship between vulnerability and ATT outcomes remains poorly understood. The concept of overlapping vulnerabilities, derived from syndemic and social determinants frameworks, emphasizes that risk factors are not independent but may interact synergistically or antagonistically to worsen outcomes. Anticipating this perspective is critical to explain why certain populations face disproportionately high TB morbidity and mortality. Addressing this gap is crucial to achieving Pillar One of the TB eradication plan proposed by the World Health Organization (WHO).[4] This plan emphasizes targeted actions aimed at individuals highly susceptible to TB and those with limited healthcare access.

Here, given the lack of studies evaluating the interaction between multiple vulnerabilities we performed a study of all adult TB cases reported to the Brazilian Information System for Notifiable Diseases (SINAN-TB) national registry between 2015 and 2023. The aims of this study were to (1) test the hypothesis that each vulnerability represents a risk factor with variable magnitude and intensity for ATT unfavorable outcomes in Brazil; (2) assess the likelihood of each specific vulnerability related to death or loss to follow-up (LTFU) in addition to the composite endpoint, unfavorable outcomes; and (3) evaluate how the superposition of interlacing vulnerabilities can further increase the risk of unfavorable ATT outcomes in our cohort of patients.

Methods

Ethics statement

All data analyzed in this study were obtained from the Brazilian Ministry of Health's qualified SINAN-TB database, available in its public ftp repository (https://datasus.saude.gov.br/). This dataset is anonymized but contains individual-level notifications that are preprocessed by the BrMOH to improve consistency and completeness. The study followed the regulations dictated by Resolutions No. 466/12 and No. 674/2022 on Research Ethics of the National Health Council, Brazil. Written informed consent for participation was not required in accordance with national legislation and institutional requirements.

Overall study design

The primary hypothesis was that vulnerable populations were at increased risk of experiencing an unfavorable ATT outcome. We performed a retrospective cohort study to test whether homelessness, pregnancy, incarceration, immigration, drug use, living with HIV, TB-Diabetes Mellitus (TB-DM), HCW status, alcohol use, tobacco use, or retreatment history at the time of TB diagnosis were associated with increased odds of unfavorable ATT outcome. To ensure data quality, duplicate registrations were removed, and consistency checks were applied before analysis. The non-vulnerable group was comprised of cases without any of the vulnerability characteristics listed at the time of diagnosis.

Additionally, we assessed whether individuals with multiple vulnerabilities experienced a higher-than-expected risk of unfavorable outcomes. Specifically, interaction analyses were conducted to evaluate both

additive and multiplicative scales. On the additive scale, we estimated the Relative Excess Risk due to Interaction (RERI), which quantifies the excess risk attributable to the joint presence of two vulnerabilities beyond the sum of their individual effects. On the multiplicative scale, we examined departure from the product of the individual effects. Together, these metrics provided complementary insights into whether and how vulnerabilities interact to shape ATT outcomes.

Children (<18 years old) were excluded because of different clinical presentations and predictors of TB outcomes. We also excluded cases without information on ATT outcome (incomplete cases) and those with non-treatment-related outcomes (e.g., change in diagnosis, ongoing treatment, transfer to another unit).

Details on the notification of TB cases on the SINAN-TB database, as well as on how we collected data from it at present in the Supplementary Methods and Supplementary Figure S1.

Vulnerability definition

In accordance with the WHO, we defined vulnerable populations as groups who have an increased risk of developing active TB.[18] The vulnerabilities evaluated in this study included homelessness, incarceration, immigration, healthcare work, drug use, alcohol use, tobacco use, pregnancy, and previous ATT history (retreatment cases), as well as biological conditions such as living with HIV and TB-DM at the time of diagnosis.[19]

We further classified the vulnerabilities into two dimensions: social and biological. This classification was based on the underlying mechanisms that increase an individual's risk of developing active TB. Social vulnerabilities, such as homelessness, incarceration, immigration, healthcare work, drug use, alcohol use, tobacco use, pregnancy, and retreatment history, were considered to arise primarily from disadvantaged socioeconomic conditions, barriers to care, or ATT discontinuity. In contrast, biological vulnerabilities, including living with HIV and TB-DM comorbidity, were defined by their association with impaired immune function and increased physiological susceptibility to TB disease.[20,21]

Substance usage (alcohol and illicit drugs) was treated as a distinct category due to its dual nature. Substance usage disorders are chronic medical conditions with biological mechanisms — such as neurochemical changes, immune modulation, and increased susceptibility to infection — that directly affect TB progression and treatment outcomes. At the same time, substance usage is shaped by social and behavioural determinants and strongly associated with delayed diagnosis, poor adherence, and loss to follow-up. For this reason, we defined it as a substance usage vulnerability, reflecting the combined biological and social components through which it contributes to adverse outcomes.

Full variable definition, including descriptions of clinical and demographic characteristics of people notified with TB on SINAN-TB are present in Supplementary Methods.

Outcome definition

An unfavorable ATT outcome was defined as TB treatment failure (positive sputum smear results at the end of treatment), LTFU (defined as an interruption of ATT for more than 30 consecutive days after the expected return date to a healthcare unit), or death (any death occurring during treatment, regardless of cause). A favourable ATT outcome was defined as cure, either clinical or bacteriological, according to national guidelines. Definitions for cure, treatment failure, LTFU, and death followed the Manual of Recommendations for the Control of TB in Brazil and are detailed in Supplementary Table S1.[22,23] Other outcomes, such as transfer to another healthcare unit, treatment modification due to drug-resistant TB, change in diagnosis, or ongoing ATT at the time of data extraction, were excluded from the analyses because the final ATT outcome could not be determined (Fig. 1).

Statistical analysis

Clinical and epidemiologic variables were summarized as frequencies and percentages (%) except for continuous variables which were reported as medians with interquartile ranges (IQR). Descriptive analyses were used to summarize the distribution and main characteristics of the: (i) non-vulnerable population, (ii) pregnant women, (iii) PDL, (iv) homeless, (v) HCW, (vi) drug users (vii) PWH and (viii) immigrants. Variables with more than 45% missing data were excluded from the analyses. To minimize bias, all other analyses used listwise deletion. We also performed a complete-case sensitivity analysis to verify the robustness of results. Covariates were selected based on literature review, clinical relevance, statistical significance in bivariate analysis, and absence of multicollinearity (variation inflation factor [VIF] < 5).[24,25]

Then, the frequency of the composite unfavorable outcomes and the individual outcomes, death and LTFU were compared between each vulnerability and non-vulnerability. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated from binary logistic regression models (Wald method).

Interaction analysis

Finally, to investigate whether co-occurring vulnerabilities produced a synergistic (increasing) or antagonistic (decreasing) effect, we assessed additive interaction between pairs of vulnerability indicators in a multivariate GLM (multivariate logistic regression), including all vulnerabilities analyzed in this study. Models were adjusted for race, sex, age, education and DOT We calculated four complementary measures. First, the

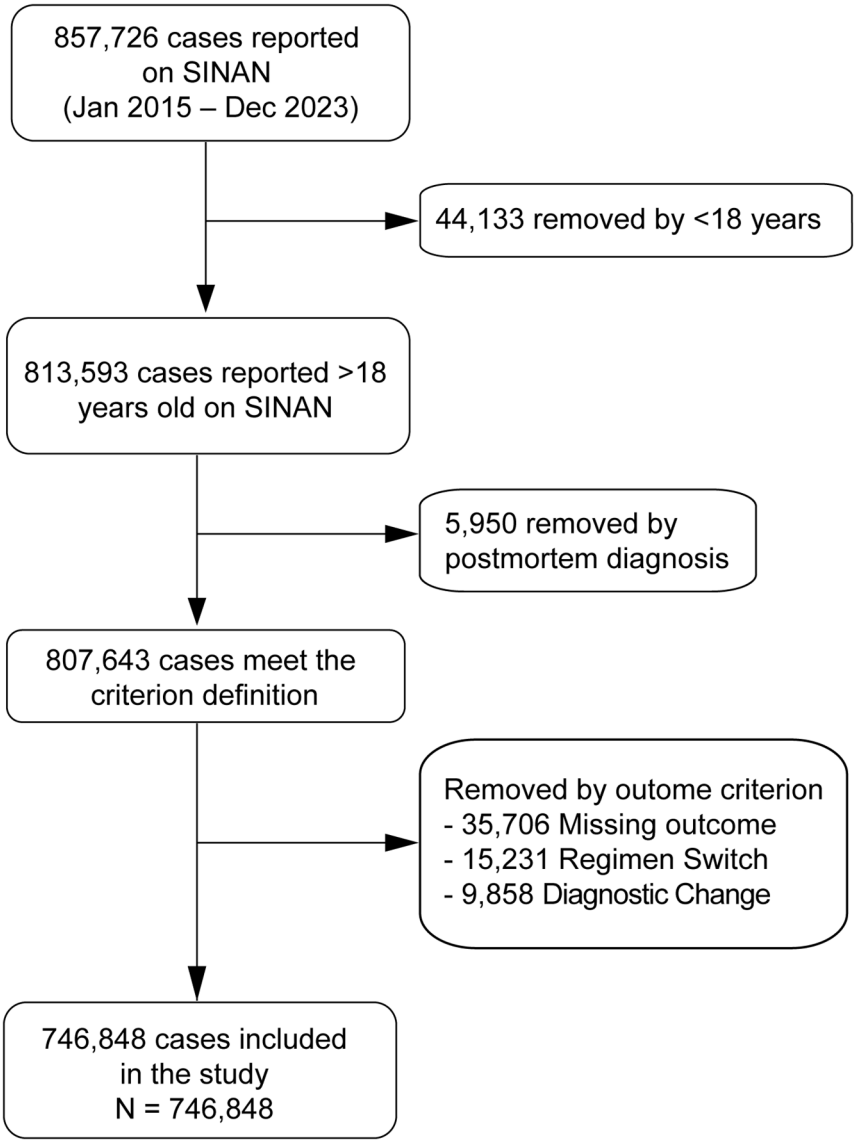

Fig. 1: **Flow chart of the TB cases notified in Brazil between 2015 and 2023 stratified according to the vulnerability condition.** Abbreviations: PWH: people with HIV; HCW: healthcare worker; PUD: people who use drugs; PDL: people deprived of their liberty; HCU: healthcare unit.

multiplicative effect (ME) evaluates whether the combined exposure departs from the product of the individual effects, capturing interaction on the multiplicative scale, being known as the interaction odds ratio. Second, the RERI quantifies the excess risk beyond the sum of the individual effects; values above zero indicate synergy, and values below zero indicate antagonism.

RERI was computed based on adjusted ORs from the GLM using the following formula:

$$RERI = OR_{11} - (OR_{10} - OR_{01}) + 1$$

where:

- OR_{11} is the odds ratio for individuals exposed to both vulnerabilities,
- OR_{10} for individuals exposed only to the first vulnerability,
- OR_{01} for those with only the second vulnerability,

For all cases the unexposed group (OR_{00}) is used as the reference. Confidence intervals for RERI were estimated using the delta method.

These measures were interpreted as follows: both a RERI >0 and ME > 1 indicated positive super-additive

interaction (i.e., synergism) on the additive and a multiplicative scale, respectively. This suggests that the combined effect exceeds the sum of individual risks; while a RERI = 0 and ME = 1 indicated an neutral interaction, in which the combined effects equal the direct sum or product of individual risks. Otherwise, a RERI < 0 and ME < 1, both indicate negative interactions (i.e., antagonism), suggesting the interaction between two variables reduces the overall risk on unfavorable outcomes. This approach enables quantification of the excess risk attributable to exposure to joint vulnerabilities, beyond what would be expected from individual contributions alone.

Furthermore, the synergy index (S), which expresses the ratio of the observed joint effect to the sum of the independent effects, with values above one indicating synergy and values below one indicating antagonism. Next, the attributable proportion (AP) estimates the fraction of risk among those with both exposures that is attributable to their interaction, providing a measure of its public health relevance. Together, these metrics provide a comprehensive assessment of whether and how co-occurring vulnerabilities interact to shape the outcome. Model suitability was checked using visual inspection (i.e., plot of the residuals).[26,27]

Results

Characteristics of the study participants

There were 857,726 TB cases notified in Brazil between 2015 and 2023. Of note, 44,240 cases were excluded among those <18-year-old, 5950 for post-mortem notification, as well as 35,706 with missing outcome data, 15,231 treatment change and 9858 change in diagnosis (Fig. 1). We categorized this population by characteristic vulnerable conditions with 351,705 vulnerable cases; including 113,723 PUD, 74,156 PDL, 63,971 PWH, 56,814 TB-DM, 27,178 homeless cases, 8495 HCW, 4035 immigrants, and 3333 pregnant women reported as TB cases during this period (Supplementary Tables S2–S9). We focused our findings on the evaluation of each population and on delineating the risk factors associated with the presence of vulnerability and unfavorable ATT outcomes.

Characteristics of the study population stratified by vulnerability were shown in Supplementary Tables S2–S9. Across all vulnerable populations, non-white individuals predominated, and lower levels of schooling (5–9 & 9–12 years) were consistently observed, with HCWs being the sole exception. Median ages ranged from younger groups like pregnant women (primarily 18–35 years; 68.8%), prisoners (72.7%) and immigrants (52.3%) to older populations such as persons living with PWH (45.2% aged 35–50 years) and individuals with TB-DM (45.7% aged 50–65 years).

Regarding addictive substance consumption, homeless individuals and PUD exhibited notably higher rates of alcohol (57.9% and 54.3%, respectively) and tobacco usage (53.0% and 64.0%, respectively). Mental illness prevalence was notably higher among homeless individuals (6.04%) and drug users (4.19%). DM was particularly less common among individuals reporting drug use (3.06%) and among those with HIV (3.11%), while also substantially more frequent among HCW (9.22%) (Supplementary Tables S2–S9).

Importantly, the way patients were notified in the system after diagnosis, along with history of prior TB with or without adequate treatment, was evaluable using the entry mode variable. Homeless individuals showed the lowest proportion of new cases (56.5%), indicating a notable tendency to re-enter TB care after previous ATT (43.5%), closely followed by PUD (32% re-treatments). Conversely, healthcare workers exhibited the highest frequency of new-case notifications (92.8%), in addition to individuals with TB-DM (87.7%) and immigrants (86.5%) (Supplementary Tables S2–S9). The utilization of DOT also varied significantly across subpopulations. PPL and immigrants demonstrated the highest DOT utilization rates (57% and 49%, respectively), while PWH and HCWs showed considerably lower DOT coverage (24% and 29%, respectively).

Vulnerabilities as a risk factor for ATT outcomes

To describe the factors populations with highest frequencies of unfavorable outcomes, bivariate comparisons among TB cases were performed (Table 1). For this analysis, we also excluded cases with outcomes reported as transfers, diagnosis, or treatment regimen switches.

The strongest bivariate association with an unfavorable ATT outcome was found among the homeless population (OR: 5.52; 95% CI: 5.38–4 = 5.66 vs. non-vulnerable group). This was followed by PWH (OR: 3.04; 95% CI: 2.99–3.10), as well as drug (OR: 2.60; 95% CI: 2.56–2.63) and alcohol (OR: 2.19; 95% CI: 2.17–2.22) use. Other factors including re-entering after previous ATT (OR: 2.64; 95% CI: 2.61–2.68), in addition to being aged >80-year-old (OR: 1.87; 95% CI: 1.81–1.94) also emerged as more common among those with unfavorable outcomes (Table 1). In contrast, DOT coverage had a strong protective effect (OR = 0.35; 95% CI: 0.34–0.36), reinforcing its importance in treatment success.

Notably, among social vulnerabilities, homelessness, drug use, and immigrant status (OR: 1.18; 95% CI: 1.10–1.26) were all positive associated with unfavorable outcomes, while PDL (OR: 0.48; 95% CI: 0.47–0.49) and HCWs (OR: 0.33; 95% CI: 0.30–0.36) had significantly lower odds of unfavorable outcomes.

Otherwise, biological vulnerabilities also showcased distinct associations. While both HIV infection and pregnancy (OR = 1.15; 95% CI: 1.06–1.24) emerged as predictors of poor ATT outcomes, in contrast, TB-DM

	Favorable outcome (n = 500,564)	Unfavorable outcome (n = 179,008)	OR [95% CI]
Age (years)			
18–35	202,058 (40.4%)	68,156 (38.1%)	Ref.
35–50	143,436 (28.7%)	56,678 (31.7%)	1.17 [1.16–1.19]
50–65	104,811 (20.9%)	33,464 (18.7%)	0.95 [0.93–0.96]
65–80	42,421 (8.47%)	15,755 (8.80%)	1.10 [1.08–1.12]
>80	7838 (1.57%)	4955 (2.77%)	1.87 [1.81–1.94]
Race			
White	150,078 (30.0%)	44,965 (25.1%)	Ref.
Non-White	350,486 (70.0%)	134,043 (74.9%)	1.28 [1.26–1.29]
Sex			
Female	155,367 (31.0%)	43,710 (24.4%)	Ref.
Male	345,197 (69.0%)	135,298 (75.6%)	1.39 [1.38–1.41]
Schooling (years)			
<5	52,429 (10.5%)	19,904 (11.1%)	Ref.
(5,9)	159,196 (31.8%)	70,480 (39.4%)	1.17 [1.14–1.19]
(9,12)	251,763 (50.3%)	83,215 (46.5%)	0.87 [0.86–0.89]
≥12	37,176 (7.43%)	5409 (3.02%)	0.38 [0.37–0.40]
Entry mode			
New Case	432,736 (86.4%)	126,590 (70.7%)	Ref.
Re enter	67,828 (13.6%)	52,418 (29.3%)	2.64 [2.61–2.68]
DOT coverage (Mean, sd)	0.42 (0.49)	0.21 (0.40)	0.35 [0.34–0.36]
Mental illness	11,009 (2.20%)	5795 (3.24%)	1.49 [1.44–1.54]
Substance usage			
Drug use	64,223 (12.8%)	49,500 (27.7%)	2.60 [2.56–2.63]
Alcohol use	81,579 (16.3%)	53,581 (29.9%)	2.19 [2.17–2.22]
Tobacco use	115,015 (23.0%)	61,142 (34.2%)	1.74 [1.72–1.76]
Social vulnerabilities			
Drug use	64,223 (12.8%)	49,500 (27.7%)	2.60 [2.56–2.63]
PDL	62,535 (12.5%)	11,621 (6.49%)	0.48 [0.47–0.49]
HCW	7588 (1.52%)	907 (0.51%)	0.33 [0.30–0.36]
Homeless	9657 (1.93%)	17,521 (9.79%)	5.52 [5.38–5.66]
Immigrants	2838 (0.57%)	1197 (0.67%)	1.18 [1.10–1.26]
Biological vulnerabilities			
Diabetes	43,756 (8.74%)	5596 (4.74%)	0.82 [0.80–0.84]
HIV	32,626 (6.52%)	31,345 (17.5%)	3.04 [2.99–3.10]
Pregnancy	2364 (0.47%)	969 (0.54%)	1.15 [1.06–1.24]

Data are presented as counts (n) and percentages (%); DOT coverage is presented as mean ± standard deviation (SD). Odds ratios (OR) and 95% confidence intervals (CI) were estimated using bivariate logistic regression; reference categories are indicated (Ref.). Abbreviations: ATT = antituberculosis treatment; DOT = directly observed therapy; PDL = people deprived of liberty (incarcerated individuals); HCW = healthcare workers; TB-DM = tuberculosis–diabetes mellitus; LTFU = loss to follow-up; SD = standard deviation.

Table 1: **Characteristics of Brazilian TB cases associated with unfavorable ATT outcomes.**

was associated with lower odds of unfavorable outcomes (OR = 0.82; 95% CI: 0.80–0.84).

Next, we evaluated the prevalence of each specific type of vulnerability within those who died or were LTFU individually, considering cure as the reference outcome. When LTFU was considered, homelessness was the major risk factor (OR_{LTFU} = 6.66; 95% CI: 6.48–6.84), followed by drug use (OR_{LTFU}: 3.46; 95% CI: 3.41–3.51), living with HIV (OR_{LTFU}: 2.35; 95% CI: 2.31–2.40), and pregnancy (OR_{LTFU}: 1.41; 95% CI: 1.308–1.53). Notably, retreatment cases (OR_{LTFU} = 3.35; 95% CI: 3.30–3.40) were also among those with highest risk of LTFU during ATT (Supplementary Table S10).

When death was used as the primary outcome, despite advanced age, living with HIV (OR_{death}: 4.60; 95% CI: 4.50–4.70) and homelessness (OR_{death}:3.44; 95% CI: 3.31–3.57) were the populations with highest frequency of mortality (Supplementary Table S11). Interestingly, while TB-DM comorbidity emerged as a protective factor against LTFU (OR_{LTFU}: 0.53; 95% CI: 0.51–0.54), it emerged as a significant bivariate association with death (OR_{death}: 1.47; 95% CI: 1.42–1.50) in the Brazilian population (Supplementary Table S11). On the other hand, DOT (OR_{LTFU}: 0.31; 95% CI: 0.30–0.32; OR_{death}: 0.45; 95% CI: 0.43–0.47), HCW (OR_{LTFU}: 0.51; 95% CI: 0.45–0.59]; OR_{death}: 0.50; 95%

CI: 0.40–0.61]) and incarceration (OR_{LTFU}: 0.68; 95% CI: 0.64–0.71]; OR_{death}: 0.43; 95% CI: 0.38–0.49]) were associated with cure in both models (Supplementary Tables S10 and S11).

Interactions among vulnerabilities impacting ATT outcomes

Our interaction analysis, including various social and biological vulnerabilities, highlights significant complexity in their combined impact on unfavorable ATT outcomes. Particularly noteworthy was the synergistic interaction between HIV infection & drug use, which substantially elevated the risk beyond their independent effects on the additive scale (RERI = 1.72 [95% CI: 1.28–2.28]), however the ME indicated an antagonist effect (0.85 [0.81–0.89]). Notably, combinations of alcohol use with tobacco smoking (RERI = 0.10 [95% CI: 0.04–0.17]), as well as living with HIV (RERI = 0.45 [95% CI: 0.23–0.73]), also showcased modest but significant superadditive interactions, while also presenting antagonist relationships on the multiplicative scale (tobacco: 0.96 [0.93–0.99], HIV = 0.88 [0.84–0.92]) (Table 2).

Conversely, certain interactions between vulnerabilities presented negative interactions or non-significant superadditive interactions, suggesting that combined vulnerabilities do not always amplify risks above their independent effects. For example, an antagonistic interaction was found between drug and alcohol use in both additive and multiplicative scales (RERI = –0.25 [95% CI: –0.35 to (–0.13)]; ME: 0.74 [0.71–0.76]), as well as immigrant status with not being incarcerated (RERI = –0.61 [95% CI: –0.08 to (–1.02)]), although ME was non-significant. Both these results indicate that the joint presence of these vulnerabilities decreased their overall risk of unfavorable ATT outcomes, compared to additively combining their independents ORs (Table 2).

Similarly, only multiplicative findings were observed to be significant for interactions between PWH & tobacco use (0.82 [0.78–0.86]), homelessness & retreatment (ME = 0.66 [0.63–0.70]), despite high baseline risks individually. Importantly, no significant superadditive relationships were found in interactions involving certain social vulnerabilities, including the homeless population (Table 2).

When focusing specifically on mortality, interactions involving PWH once again showed particularly strong synergistic effects, especially with substance usage. The interaction between PWH & drug use markedly increased the risk of death (RERI = 2.76 [95% CI: 1.92–3.86], no significant multiplicative interaction), consistent with the pattern observed in overall unfavorable outcomes. Similarly, interactions of HIV infection & alcohol use (RERI = 0.46 [95% CI: 0.04–1.01]) demonstrated significant superadditive effects on mortality, while antagonistic results were found in the ME: 0.76 [0.71–0.81]. Conversely, tobacco use significantly attenuated the mortality risk associated with HIV infection (RERI = –0.58 [95% CI: –0.91 to (–0.21)], ME = 0.72 [0.67–0.76]), indicating a protective or antagonistic interaction distinct from general unfavorable outcomes. Furthermore, patients with a habit of both tobacco and alcohol usage also showcased a further significant increase in risk of mortality (RERI = 0.55 [95% CI: 0.43–0.68]; ME = 1.16 [1.11–1.22], synergistic on both scales) (Table 3).

Additionally, not having TB-DM, also possessed important interactions with both social and biological vulnerability. While the absence of diabetes was shown to increase the risk of death among PWH (RERI = 1.12 [95% CI: 0.56–1.64]; ME = 1.32 [1.18–1.48], synergistic on both scales), when combined with certain consumption habits, the lack of this comorbidity significantly decreased odds of mortality among those using drugs (RERI = –0.28 [95% CI: –0.5 to (–0.09)]; OR_INT = 0.85 [0.76–0.97]) and tobacco (RERI = –0.25 [95% CI: –0.34 to (–0.16)]; OR_INT = 0.82 [0.76–0.88]), on both scales (Table 3).

Finally, when focusing on LTFU cases, we found significant positive interactions including retreatment & not being incarcerated (RERI = 3.12 [95% CI: 2.41–4.25]; OR_INT = 1.94 [1.85–2.05], synergistic on both scales), underscoring that previously treated patients outside institutional settings face substantially increased risk of LTFU. Additionally, the interaction between living with HIV & drug use remained strongly synergistic (RERI = 1.98 [95% CI: 1.39–2.76], no significant multiplicative interaction), consistent with findings on unfavorable outcomes and mortality. Also, patients without TB-DM comorbidity but also consumed alcohol also possessed a significantly higher risk of LTFU (RERI = 0.29 [95% CI: 0.17–0.40]; OR_INT = 1.14 [1.04–1.23], synergistic on both scales). Conversely, interactions between drug & alcohol use (RERI = –0.33 [95% CI: –0.52 to (–0.12)]; OR_INT = 0.76 [0.73–0.79], antagonistic on both scales), as well as drug use with the absence of TB-DM (RERI = –0.62 [95% CI: –0.96–(–0.31)]; OR_INT = 0.71 [0.65–0.79], **antagonistic on both scales**) exhibited significant negative interactions, suggesting antagonistic effects specific to LTFU outcomes (Table 4).

Discussion

The devastating impact of TB in the public health system of Brazil is substantially greater in socially vulnerable populations than those without any vulnerability.[2,19] Using a large, nationally representative dataset of all available persons diagnosed with TB in Brazil between 2015 and 2023, the present study fills an important knowledge gap between the overlapping of both biological and social vulnerabilities, alone and in combination, influence the risk of with unfavorable ATT outcomes.

Composite unfavorable outcome					
Interactions	Odds ratio [95% CI]	RERI	AP	SI	Multiplicative scale
Substance usage					
Tobacco use & alcohol use		**0.1 [0.04–0.17]**	**0.05 [0.02–0.08]**	**1.12 [1.05–1.19]**	**0.96 [0.93–0.99]**
Effect of tobacco use among non-alcohol users (A+ | B–)	1.35 [1.28–1.43]				
Effect of alcohol use among non-tobacco users (B+ | A–)	1.5 [1.41–1.59]				
Effect of tobacco use among alcohol users (A+ | B+)	1.3 [1.23–1.38]				
Effect of alcohol use among tobacco users (B+ | A+)	1.44 [1.36–1.53]				
Tabacco use & drug use		0.02 [−0.09 to 0.15]	0.01 [−0.04 to 0.05]	1.01 [0.95–1.08]	0.85 [0.83–0.88]
Effect of tobacco use among non-alcohol users (A+ | B–)	1.35 [1.28–1.43]				
Effect of alcohol use among non-tobacco users (B+ | A–)	2.42 [2.22–2.63]				
Effect of tobacco use among alcohol users (A+ | B+)	1.15 [1.09–1.23]				
Effect of alcohol use among tobacco users (B+ | A+)	2.06 [1.89–2.25]				
Drug use & alcohol use		−0.25 [−0.35 to −0.13]	−0.09 [−0.14 to −0.05]	0.87 [0.81–0.93]	0.74 [0.71–0.76]
Effect of drug use among non-alcohol users (A+ | B–)	2.42 [2.22–2.63]				
Effect of alcohol use among non-drug users (B+ | A–)	1.5 [1.41–1.59]				
Effect of drug use among alcohol users (A+ | B+)	1.78 [1.63–1.94]				
Effect of alcohol use among drug users (B+ | A+)	1.1 [1.03–1.18]				
Social vulnerabilities					
Not PPL & retreatment		2.25 [1.74–3.04]	0.49 [0.43–0.51]	2.64 [2.48–2.81]	1.63 [1.55–1.71]
Effect of not PPL among new cases (A+ | B–)	1.78 [1.73–1.83]				
Effect of retreatment among PPL (B+ | A–)	1.59 [1.28–1.98]				
Effect of not PPL among retreatment (A+ | B+)	2.9 [2.78–3.02]				
Effect of retreatment among not PPL (B+ | A+)	2.6 [2.1–3.21]				
Not PPL & immigrants		**0.61 [0.08–1.02]**	**0.22 [0.03–0.36]**	**1.53 [1.04–2.24]**	1.13 [0.82–1.55]
Effect of not PPL among non-immigrants (A+ | B–)	1.78 [1.73–1.83]				
Effect of immigrants among PPL (B+ | A–)	1.37 [1–1.89]				
Effect of not PPL among immigrants (A+ | B+)	1.55 [1.43–1.69]				
Effect of immigrants among not PPL (B+ | A+)	2.6 [2.1–3.21]				
Not PPL & pregnancy		−1 [−4.52 to 0.98]	−0.67 [−2.97 to 0.07]	0.33 [0.04–3.08]	0.49 [0.23–1.05]
Effect of not PPL among non-pregnancy (A+ | B–)	1.78 [1.73–1.83]				
Effect of pregnancy among PPL (B+ | A–)	1.71 [0.49–5.95]				
Effect of not PPL among pregnancy (A+ | B+)	0.87 [0.41–1.87]				
Effect of pregnancy among not PPL (B+ | A+)	0.84 [0.29–2.41]				
Immigrants & retreatment		−0.06 [−0.39 to 0.55]	−0.03 [−0.37 to 0.1]	0.93 [0.58–1.5]	0.87 [0.71–1.06]
Effect of immigrants among new cases (A+ | B–)	1.37 [1–1.89]				
Effect of retreatment among non-immigrants (B+ | A–)	1.59 [1.28–1.98]				
Effect of immigrants among retreatment (A+ | B+)	1.19 [0.82–1.73]				
Effect of retreatment among immigrants (B+ | A+)	1.39 [1.04–1.84]				
Immigrants & pregnancy		1.02 [−1.48 to 9.17]	0.33 [−1.01 to 0.9]	1.94 [0.72–5.21]	1.32 [0.69–2.54]
Effect of immigrants among non-pregnancy (A+ | B–)	1.37 [1–1.89]				
Effect of pregnancy among non-immigrants (B+ | A–)	1.71 [0.49–5.95]				
Effect of immigrants among pregnancy (A+ | B+)	1.81 [0.88–3.72]				
Effect of pregnancy among immigrants (B+ | A+)	2.26 [0.58–8.75]				
Homelessness & immigrants		−0.45 [−1.08 to 0.45]	−0.13 [−0.44 to 0.07]	0.84 [0.62–1.15]	0.71 [0.56–0.91]
Effect of homelessness among non-immigrants (A+ | B–)	3.5 [3.38–3.63]				
Effect of immigrants among non-homelessness (B+ | A–)	1.37 [1–1.89]				
Effect of homelessness among immigrants (A+ | B+)	2.49 [1.95–3.19]				
Effect of immigrants among homelessness (B+ | A+)	0.98 [0.74–1.29]				
Homelessness & pregnancy		−0.28 [−2.03 to 8.8]	−0.07 [−2.26 to 0.06]	0.91 [0.3–2.75]	0.66 [0.45–0.96]
Effect of homelessness among non-pregnancy (A+ | B–)	3.5 [3.38–3.63]				
Effect of pregnancy among non-homelessness (B+ | A–)	1.71 [0.49–5.95]				
Effect of homelessness among pregnancy (A+ | B+)	2.3 [1.57–3.36]				
Effect of pregnancy among homelessness (B+ | A+)	1.12 [0.31–4.05]				
Homelessness & retreatment		−0.4 [−0.78 to 0.23]	−0.11 [−0.29 to 0.02]	0.87 [0.72–1.06]	0.66 [0.63–0.7]
Effect of homelessness among new cases (A+ | B–)	3.5 [3.38–3.63]				
Effect of retreatment among non-homelessness (B+ | A–)	1.59 [1.28–1.98]				
Effect of homelessness among retreatment (A+ | B+)	2.32 [2.22–2.43]				
Effect of retreatment among homelessness (B+ | A+)	1.06 [0.85–1.32]				

(Table 2 continues on next page)

Composite unfavorable outcome					
Interactions	Odds ratio [95% CI]	RERI	AP	SI	Multiplicative scale
(Continued from previous page)					
Not HCW & retreatment		0.26 [−0.1 to 0.56]	0.09 [−0.03 to 0.19]	1.15 [0.95–1.38]	0.88 [0.71–1.08]
Effect of not HCW among new cases (A+ | B−)	2.17 [2.01–2.35]				
Effect of retreatment among HCW (B+ | A−)	1.59 [1.28–1.98]				
Effect of not HCW among retreatment (A+ | B+)	1.9 [1.56–2.32]				
Effect of retreatment among not HCW (B+ | A+)	1.39 [1.33–1.46]				
Biological vulnerabilities					
HIV & alcohol use		**0.45 [0.23–0.73]**	**0.11 [0.06–0.16]**	**1.18 [1.09–1.28]**	**0.88 [0.84–0.92]**
Effect of HIV among non-alcohol users (A+ | B−)	2.99 [2.71–3.3]				
Effect of alcohol use among non–HIV (B+ | A−)	1.5 [1.41–1.59]				
Effect of HIV among alcohol users (A+ | B+)	1.32 [1.22–1.42]				
Effect of alcohol use among HIV (B+ | A+)	2.63 [2.37–2.93]				
HIV & tobacco use		−0.04 [−0.21 to 0.16]	−0.01 [−0.07 to 0.04]	0.98 [0.91–1.06]	0.82 [0.78–0.86]
Effect of HIV AMONG NON-TOBACCO Users (A+ | B−)	2.99 [2.71–3.3]				
Effect of tobacco use among non–HIV (B+ | A−)	1.35 [1.28–1.43]				
Effect of HIV among tobacco users (A+ | B+)	2.44 [2.2–2.72]				
Effect of tobacco use among HIV (B+ | A+)	1.1 [1.03–1.18]				
HIV & drug use		**1.72 [1.28–2.28]**	**0.28 [0.23–0.32]**	**1.5 [1.4–1.62]**	**0.85 [0.81–0.89]**
Effect of HIV among non-drug users (A+ | B−)	2.99 [2.71–3.3]				
Effect of drug use among non–HIV (B+ | A−)	2.42 [2.22–2.63]				
Effect of HIV among drug users (A+ | B+)	2.54 [2.27–2.83]				
Effect of drug use among HIV (B+ | A+)	2.05 [1.86–2.25]				
HIV & not diabetes		−0.12 [−0.43 to 0.16]	−0.04 [−0.15 to 0.05]	0.94 [0.82–1.09]	0.92 [0.83–1.02]
Effect of HIV among diabetes (A+ | B−)	2.99 [2.71–3.3]				
Effect of not diabetes among non–HIV (B+ | A−)	1.07 [1.04–1.1]				
Effect of HIV among not diabetes (A+ | B+)	2.76 [2.69–2.82]				
Effect oF NOT DIABETES AMONG HIV (B+ | A+)	0.98 [0.89–1.08]				
Not diabetes & drug use		−0.17 [−0.38 to 0.03]	−0.07 [−0.16 to 0.01]	0.89 [0.77–1.02]	0.90 [0.83–0.98]
Effect of not diabetes among non-drug users (A+ | B−)	1.07 [1.04–1.1]				
Effect of DRUG USE AMONG DIABetes (B+ | A−)	2.42 [2.22–2.63]				
Effect of not diabetes among drug users (A+ | B+)	0.96 [0.88–1.05]				
Effect of drug use among not diabetes (B+ | A+)	2.17 [2.11–2.23]				
Not diabetes & tobacco use		−0.07 [−0.15 to 0]	−0.05 [−0.11 to 0]	0.83 [0.7–0.99]	0.93 [0.88–0.99]
Effect of not diabetes among non-tobacco users (A+ | B−)	1.07 [1.04–1.1]				
Effect of tobacco use among diabetes (B+ | A−)	1.35 [1.28–1.43]				
Effect of not diabetes among tobacco users (A+ | B+)	1 [0.95–1.05]				
Effect of tobacco use among not diabetes (B+ | A+)	1.26 [1.24–1.29]				
Not diabetes & alcohol use		0.07 [−0.02, 0.16]	0.04 [−0.01, 0.1]	1.12 [0.96, 1.31]	1.02 [0.96, 1.09]
Effect of not diabetes among non-alcohol users (A+ | B−)	1.07 [1.04–1.1]				
Effect of alcohol use among diabetes (B+ | A−)	1.5 [1.41, 1.59]				
Effect of not diabetes among alcohol users (A+ | B+)	1.09 [1.03, 1.16]				
Effect of alcohol use among not diabetes (B+ | A+)	1.53 [1.49, 1.57]				
Pregnancy & retreatment		0.92 [−1.09 to 7.97]	0.28 [−0.76 to 0.72]	1.7 [1.25–2.33]	1.18 [0.99–1.42]
Effect of pregnancy among new cases (A+ | B−)	1.71 [0.49–5.95]				
Effect of retreatment among non-pregnancy (B+ | A−)	1.59 [1.28–1.98]				
Effect of pregnancy among retreatment (A+ | B+)	2.02 [0.58–7.1]				
Effect of retreatment among pregnancy (B+ | A+)	1.88 [1.42–2.5]				

This table presents results from an interaction analysis assessing how overlapping vulnerabilities (e.g., tobacco use, alcohol use, homelessness, pregnancy, HIV) jointly influence the likelihood of composite unfavorable outcomes. Each main row shows the overall interaction measure (Odds Ratio [95% CI]) plus four interaction metrics: RERI (Relative Excess Risk due to Interaction), AP (Attributable Proportion), SI (Synergy Index), and a measure on the multiplicative scale. Subsequent rows detail the effect of each vulnerability alone (when the other vulnerability is absent). RERI and AP values above zero indicate positive interaction (synergy) on the additive scale, whereas SI and multiplicative measures above 1 indicate positive interaction (synergy) on the multiplicative scale. Values below these thresholds indicate antagonism.

Table 2: **Interaction effects of overlapping vulnerabilities on composite unfavorable ATT outcomes.**

Death outcome

Interactions	Odds Ratio [95% CI]	RERI	AP	SI	Multiplicative scale
Substance usage					
Tobacco use & alcohol use		**0.55 [0.43–0.68]**	**0.22 [0.18–0.25]**	**1.57 [1.45–1.71]**	**1.16 [1.11–1.22]**
Effect of tobacco use among non-alcohol users (A+ | B–)	1.32 [1.23–1.41]				
Effect of alcohol use among non-tobacco users (B+ | A–)	1.64 [1.52–1.77]				
Effect of tobacco use among alcohol users (A+ | B+)	1.53 [1.42–1.65]				
Effect of alcohol use among tobacco users (B+ | A+)	1.44 [1.36–1.53]				
Tabacco use & drug use		0.03 [−0.09 to 0.17]	0.01 [−0.06 to 0.07]	1.02 [0.91–1.16]	0.91 [0.86–0.97]
Effect of tobacco use among non-alcohol users (A+ | B–)	1.32 [1.23–1.41]				
Effect of alcohol use among non-tobacco users (B+ | A–)	1.7 [1.5–1.93]				
Effect of tobacco use among alcohol users (A+ | B+)	1.2 [1.1–1.31]				
Effect of alcohol use among tobacco users (B+ | A+)	1.55 [1.36–1.76]				
Drug use & alcohol use		−0.02 [−0.15 to 0.14]	−0.01 [−0.08 to 0.04]	0.98 [0.88–1.1]	0.83 [0.78–0.88]
Effect of drug use among non-alcohol users (A+ | B–)	1.7 [1.5–1.93]				
Effect of alcohol use among non-drug users (B+ | A–)	1.64 [1.52–1.77]				
Effect of drug use among alcohol users (A+ | B+)	1.41 [1.24–1.61]				
Effect of alcohol use among drug users (B+ | A+)	1.36 [1.24–1.5]				
Social vulnerabilities					
Not PPL & retreatment		**1.03 [0.46–2.26]**	**0.3 [0.09–0.39]**	**1.75 [1.36–2.24]**	**1.34 [1.2–1.51]**
Effect of not PPL among new cases (A+ | B–)	2.25 [2.12–2.39]				
Effect of retreatment among PPL (B+ | A–)	1.13 [0.76–1.67]				
Effect of not PPL among retreatment (A+ | B+)	3.02 [2.73–3.34]				
Effect of retreatment among not PPL (B+ | A+)	1.52 [1.04–2.21]				
Not PPL & Immigrants		0.26 [−1.02 to 1.07]	0.08 [−0.32 to 0.32]	1.13 [0.69–1.87]	0.84 [0.48–1.47]
Effect of not PPL among non-immigrants (A+ | B–)	2.25 [2.12–2.39]				
Effect of Immigrants among PPL (B+ | A–)	1.7 [0.97–2.99]				
Effect of not PPL among immigrants (A+ | B+)	1.89 [1.08–3.29]				
Effect of Immigrants among not PPL (B+ | A+)	1.43 [1.25–1.64]				
Not PPL & pregnancy		−2.24 [−24.16–7.3]	−1.52 [−14.32–2.34]	0.17 [0–29.62]	0.27 [0.07–1]
Effect of not PPL among non-pregnancy (A+ | B–)	2.25 [2.12–2.39]				
Effect of pregnancy among PPL (B+ | A–)	2.46 [0.24–25.44]				
Effect of not PPL among pregnancy (A+ | B+)	0.6 [0.16–2.25]				
Effect of pregnancy among not PPL (B+ | A+)	0.65 [0.08–5.67]				
Immigrants & retreatment		−0.16 [−0.91 to 1.09]	−0.09 [−0.88 to 0.18]	0.81 [0.3–2.18]	0.87 [0.61–1.25]
Effect of immigrants among new cases (A+ | B–)	1.7 [0.97–2.99]				
Effect of retreatment among non-immigrants (B+ | A–)	1.13 [0.76–1.67]				
Effect of immigrants among retreatment (A+ | B+)	1.48 [0.76–2.9]				
Effect of retreatment among immigrants (B+ | A+)	0.98 [0.59–1.63]				
Immigrants & pregnancy		5.15 [−11.68–88.07]	0.62 [−1.61 to 1.62]	3.38 [0.89–12.87]	1.98 [0.61–6.4]
Effect of immigrants among non-pregnancy (A+ | B–)	1.7 [0.97–2.99]				
Effect of pregnancy among non-immigrants (B+ | A–)	2.46 [0.24–25.44]				
Effect of immigrants among pregnancy (A+ | B+)	3.38 [0.94–12.08]				
Effect of pregnancy among immigrants (B+ | A+)	4.88 [0.45–53.22]				
Homelessness & immigrants		0.12 [−0.88 to 1.83]	0.04 [−0.45 to 0.26]	1.05 [0.64–1.73]	0.78 [0.51–1.17]
Effect of homelessness among non-immigrants (A+ | B–)	2.58 [2.44–2.73]				
Effect of immigrants among non-homelessness (B+ | A–)	1.7 [0.97–2.99]				
Effect of homelessness among immigrants (A+ | B+)	2 [1.33–3.01]				
Effect of immigrants among homelessness (B+ | A+)	1.32 [0.81–2.15]				
Homelessness & pregnancy		0.8 [−18.02–45.08]	0.17 [−4.86 to 1.64]	1.26 [0.35–4.58]	0.76 [0.38–1.52]
Effect of homelessness among non-pregnancy (A+ | B–)	2.58 [2.44–2.73]				
Effect of pregnancy among non-homelessness (B+ | A–)	2.46 [0.24–25.44]				
Effect of homelessness among pregnancy (A+ | B+)	1.97 [0.99–3.93]				
Effect of pregnancy among homelessness (B+ | A+)	1.88 [0.18–19.85]				
Homelessness & retreatment		−0.45 [−0.72 to 0.31]	−0.2 [−0.63 to −0.02]	0.74 [0.46–1.18]	0.78 [0.71–0.85]
Effect of homelessness among new cases (A+ | B–)	2.58 [2.44–2.73]				
Effect of retreatment among non-homelessness (B+ | A–)	1.13 [0.76–1.67]				
Effect of homelessness among retreatment (A+ | B+)	2 [1.86–2.15]				
Effect of retreatment among homelessness (B+ | A+)	0.88 [0.59–1.31]				

(Table 3 continues on next page)

Death outcome					
Interactions	Odds Ratio [95% CI]	RERI	AP	SI	Multiplicative scale
(Continued from previous page)					
Not HCW & retreatment		−0.17 [−0.72 to 0.22]	−0.07 [−0.3 to 0.09]	0.89 [0.66–1.2]	0.87 [0.6–1.27]
Effect of not HCW among new cases (A+ | B−)	2.41 [2.12–2.74]				
Effect of retreatment among HCW (B+ | A−)	1.13 [0.76–1.67]				
Effect of not HCW among retreatment (A+ | B+)	2.1 [1.47–3]				
Effect of retreatment among not HCW (B+ | A+)	0.98 [0.88–1.1]				
Biological vulnerabilities					
HIV & alcohol use		**0.46 [0.04–1.01]**	**0.08 [0–0.15]**	**1.11 [1.01–1.22]**	**0.76 [0.71–0.81]**
Effect of HIV among non-alcohol users (A+ | B−)	4.64 [4.14–5.21]				
Effect of alcohol use among non–HIV (B+ | A−)	1.64 [1.52–1.77]				
Effect of HIV among alcohol users (A+ | B+)	3.51 [3.09–3.98]				
Effect of alcohol use among HIV (B+ | A+)	1.32 [1.22–1.42]				
HIV & tobacco use		**−0.58 [−0.91 to −0.21]**	**−0.13 [−0.23 to −0.05]**	**0.85 [0.77–0.95]**	**0.72 [0.67–0.76]**
Effect of HIV among non-tobacco users (A+ | B−)	4.64 [4.14–5.21]				
Effect of tobacco use among non–HIV (B+ | A−)	1.32 [1.23–1.41]				
Effect of HIV among tobacco users (A+ | B+)	3.33 [2.93–3.77]				
Effect of tobacco use among HIV (B+ | A+)	0.94 [0.86–1.03]				
HIV & drug use		**2.76 [1.92–3.86]**	**0.34 [0.27–0.4]**	**1.64 [1.46–1.83]**	**1.03 [0.96–1.1]**
Effect of HIV among non-drug users (A+ | B−)	4.64 [4.14–5.21]				
Effect of drug use among non–HIV (B+ | A−)	1.7 [1.5–1.93]				
Effect of HIV among drug users (A+ | B+)	4.77 [4.17–5.44]				
Effect of drug use among HIV (B+ | A+)	1.75 [1.52–2]				
HIV & not diabetes		**1.12 [0.56–1.64]**	**0.2 [0.1–0.29]**	**1.31 [1.13–1.52]**	**1.32 [1.18–1.48]**
Effect of HIV among diabetes (A+ | B−)	4.64 [4.14–5.21]				
Effect of not diabetes among non–HIV (B+ | A−)	0.93 [0.9–0.96]				
Effect of HIV among not diabetes (A+ | B+)	6.13 [5.95–6.32]				
Effect of not diabetes among HIV (B+ | A+)	1.23 [1.09–1.38]				
Not diabetes & drug use		**−0.28 [−0.5 to −0.09]**	**−0.21 [−0.37 to −0.06]**	**0.56 [0.39–0.79]**	**0.85 [0.76–0.97]**
Effect of not diabetes among non-drug users (A+ | B−)	0.93 [0.9–0.96]				
Effect of drug use among diabetes (B+ | A−)	1.7 [1.5–1.93]				
Effect of not diabetes among drug users (A+ | B+)	0.79 [0.7–0.9]				
Effect of drug use among not diabetes (B+ | A+)	1.45 [1.37–1.54]				
Not diabetes & tobacco use		−0.25 [−0.34 to −0.16]	−0.25 [−0.34 to −0.16]	1.2 [0.9–1.4]	0.82 [0.76–0.88]
Effect of not diabetes among non-tobacco users (A+ | B−)	0.93 [0.9–0.96]				
Effect of tobacco use among diabetes (B+ | A−)	1.32 [1.23–1.41]				
Effect of not diabetes among tobacco users (A+ | B+)	0.76 [0.71–0.81]				
Effect of tobacco use among not diabetes (B+ | A+)	1.07 [1.04–1.11]				
Not diabetes & alcohol use		−0.03 [−0.15 to 0.09]	−0.02 [−0.1 to 0.06]	0.95 [0.77–1.19]	1.01 [0.94–1.1]
Effect of not diabetes among non-alcohol users (A+ | B−)	0.93 [0.9–0.96]				
Effect of alcohol use among diabetes (B+ | A−)	1.64 [1.52–1.77]				
Effect of not diabetes among alcohol users (A+ | B+)	0.94 [0.87–1.02]				
Effect of alcohol use among not diabetes (B+ | A+)	1.66 [1.6–1.72]				
Pregnancy & retreatment		−0.48 [−21.6–18.46]	−0.23 [−5.14 to 3.95]	0.7 [0.21–2.36]	1.18 [0.99–1.42]
Effect of pregnancy among new cases (A+ | B−)	2.46 [0.24–25.44]				
Effect of retreatment among non-pregnancy (B+ | A−)	1.13 [0.76–1.67]				
Effect of pregnancy among retreatment (A+ | B+)	1.87 [0.18–19.87]				
Effect of retreatment among pregnancy (B+ | A+)	0.86 [0.49–1.51]				

T This table presents results from an interaction analysis assessing how overlapping vulnerabilities (e.g., tobacco use, alcohol use, homelessness, pregnancy, HIV) jointly influence the likelihood of composite unfavorable outcomes. Each main row shows the overall interaction measure (Odds Ratio [95% CI]) plus four interaction metrics: RERI (Relative Excess Risk due to Interaction), AP (Attributable Proportion), SI (Synergy Index), and a measure on the multiplicative scale. Subsequent rows detail the effect of each vulnerability alone (when the other vulnerability is absent)). RERI and AP values above zero indicate positive interaction (synergy) on the additive scale, whereas SI and multiplicative measures above 1 indicate positive interaction (synergy) on the multiplicative scale. Values below these thresholds indicate antagonism.

Table 3: **Interaction effects of overlapping vulnerabilities on TB mortality.**

LTFU outcome					
Interactions	Odds ratio [95% CI]	RERI	AP	SI	Multiplicative scale
Substance usage					
Tobacco use & alcohol use		**−0.09 [−0.14, −0.03]**	**−0.06 [−0.1, −0.02]**	**0.86 [0.77, 0.96]**	**0.89 [0.86, 0.92]**
Effect of tobacco use among non-alcohol users (A+ | B−)	1.33 [1.24, 1.44]				
Effect of alcohol use among non-tobacco users (B+ | A−)	1.31 [1.2, 1.42]				
Effect of tobacco use among alcohol users (A+ | B+)	1.53 [1.42, 1.65]				
Effect of alcohol use among tobacco users (B+ | A+)	1.19 [1.1, 1.28]				
Combination tobacco use & alcohol use	1.55 [1.41, 1.71]				
Tabacco use & drug use		−0.03 [−0.22, 0.18]	−0.01 [−0.07, 0.04]	0.99 [0.91, 1.07]	0.82 [0.79, 0.85]
Effect of tobacco use among non-alcohol users (A+ | B−)	1.33 [1.24, 1.44]				
Effect of alcohol use among non-tobacco users (B+ | A−)	3.21 [2.9, 3.56]				
Effect of tobacco use among alcohol users (A+ | B+)	1.09 [1.01, 1.19]				
Effect of alcohol use among tobacco users (B+ | A+)	2.63 [2.38, 2.92]				
Combined tobacco & alcohol use A+ & B+	3.52 [3.14, 3.94]				
Drug use & alcohol use		−0.33 [−0.52, −0.12]	−0.1 [−0.17, −0.04]	0.87 [0.8, 0.95]	0.76 [0.73, 0.79]
Effect of drug use among non-alcohol users (A+ | B−)	1.7 [1.5, 1.93]				
Effect of alcohol use among non-drug users (B+ | A−)	3.21 [2.9, 3.56]				
Effect of drug use among alcohol users (A+ | B+)	2.44 [2.2, 2.71]				
Effect of alcohol use among drug users (B+ | A+)	0.99 [0.91, 1.09]				
Combined drug & alcohol use A+ & B+	3.19 [2.85, 3.58]				
Social vulnerabilities					
Not PPL & retreatment		**3.12 [2.41, 4.25]**	**0.57 [0.52, 0.59]**	**3.3 [3.09, 3.52]**	**1.94 [1.85, 2.05]**
Effect of not PPL among new cases (A+ | B−)	1.66 [1.61, 1.71]				
Effect of retreatment among PPL (B+ | A−)	1.7 [1.33, 2.16]				
Effect of not PPL among retreatment (A+ | B+)	3.23 [3.09, 3.38]				
Effect of retreatment among not PPL (B+ | A+)	3.3 [2.6, 4.19]				
Combined not PPL & retreatment A+ & B+	5.48 [4.31, 6.97]				
Not PPL & immigrants		**0.79 [0.22, 1.22]**	**0.29 [0.08, 0.43]**	**1.83 [1.13, 2.98]**	**1.28 [0.9, 1.83]**
Effect of not PPL among non-immigrants (A+ | B−)	1.66 [1.61, 1.71]				
Effect of immigrants among PPL (B+ | A−)	1.28 [0.9, 1.84]				
Effect of not PPL among immigrants (A+ | B+)	2.13 [1.49, 3.04]				
Effect of immigrants among not PPL (B+ | A+)	1.64 [1.49, 1.81]				
Combined not PPL & immigrants A+ & B+	2.73 [2.46, 3.02]				
Not PPL & pregnancy		−0.54 [−4.01, 2.12]	−0.37 [−2.96, 0.56]	0.46 [0.04, 6.06]	0.66 [0.28, 1.57]
Effect of not PPL among non-pregnancy (A+ | B−)	1.66 [1.61, 1.71]				
Effect of pregnancy among PPL (B+ | A−)	1.33 [0.32, 5.56]				
Effect of not PPL among pregnancy (A+ | B+)	1.09 [0.46, 2.61]				
Effect of pregnancy among not PPL (B+ | A+)	0.88 [0.26, 2.92]				
Combined not PPL & pregnancy A+ & B+	1.46 [0.44, 4.85]				
Immigrants & retreatment		−0.13 [−0.48, 0.56]	−0.07 [−0.49, 0.07]	0.86 [0.49, 1.52]	0.85 [0.68, 1.05]
Effect of immigrants among new cases (A+ | B−)	1.28 [0.9, 1.84]				
Effect of retreatment among non-immigrants (B+ | A−)	1.7 [1.33, 2.16]				
Effect of immigrants among retreatment (A+ | B+)	1.09 [0.72, 1.64]				
Effect of retreatment among immigrants (B+ | A+)	1.44 [1.05, 1.97]				
Combined immigrants & retreatment A+ & B+	1.84 [1.15, 2.96]				
Immigrants & pregnancy		0.49 [−2.39, 7.55]	0.23 [−1.98, 1.46]	1.79 [0.43, 7.46]	1.23 [0.61, 2.49]
Effect of immigrants among non-pregnancy (A+ | B−)	1.28 [0.9, 1.84]				
Effect of pregnancy among non-immigrants (B+ | A−)	1.33 [0.32, 5.56]				
Effect of immigrants among pregnancy (A+ | B+)	1.58 [0.73, 3.44]				
Effect of pregnancy among immigrants (B+ | A+)	1.64 [0.35, 7.64]				
Combined immigrants & pregnancy A+ & B+	2.1 [0.44, 10.1]				
Homelessness & immigrants		−0.87 [−1.59, 0.23]	−0.24 [−0.65, 0]	0.75 [0.52, 1.07]	0.67 [0.51, 0.88]
Effect of homelessness among non-immigrants (A+ | B−)	4.16 [4, 4.33]				
Effect of immigrants among non-homelessness (B+ | A−)	1.28 [0.9, 1.84]				
Effect of homelessness among immigrants (A+ | B+)	2.78 [2.13, 3.64]				
Effect of immigrants among homelessness (B+ | A+)	0.86 [0.62, 1.18]				
Combined immigrants & pregnancy A+ & B+	3.57 [2.6, 4.89]				

(Table 4 continues on next page)

LTFU outcome					
Interactions	Odds ratio [95% CI]	RERI	AP	SI	Multiplicative scale
(Continued from previous page)					
Homelessness & pregnancy		−1.1 [−2.97, 9.15]	−0.33 [−4.2, −0.2]	0.68 [0.14, 3.24]	0.61 [0.41, 0.91]
Effect of homelessness among non-pregnancy (A+ | B−)	4.16 [4, 4.33]				
Effect of pregnancy among non-homelessness (B+ | A−)	1.33 [0.32, 5.56]				
Effect of homelessness among pregnancy (A+ | B+)	2.54 [1.71, 3.78]				
Effect of pregnancy among homelessness (B+ | A+)	0.81 [0.19, 3.51]				
Combined homelessness & pregnancy (A+ & B+)	3.39 [0.79, 14.61]				
Homelessness & retreatment		−0.73 [−1.21, 0.09]	−0.18 [−0.42, −0.02]	0.81 [0.65, 1.02]	0.58 [0.55, 0.62]
Effect of homelessness among new cases (A+ | B−)	4.16 [4, 4.33]				
Effect of retreatment among non-homelessness (B+ | A−)	1.7 [1.33, 2.16]				
Effect of homelessness among retreatment (A+ | B+)	4.16 [4, 4.33]				
Effect of retreatment among homelessness (B+ | A+)	0.99 [0.77, 1.27]				
Combined homelessness & retreatment (A+ & B+)	4.13 [3.22, 5.29]				
Not HCW & retreatment		0.33 [−0.11, 0.68]	0.11 [−0.03, 0.22]	1.19 [0.95, 1.49]	0.88 [0.7, 1.12]
Effect of not HCW among new cases (A+ | B−)	2.06 [1.87, 2.27]				
Effect of retreatment among HCW (B+ | A−)	1.7 [1.33, 2.16]				
Effect of not HCW among retreatment (A+ | B+)	1.82 [1.46, 2.27]				
Effect of retreatment among not HCW (B+ | A+)	1.5 [1.43, 1.57]				
Combined not HCW & retreatment (A+ & B+)	3.09 [2.77, 3.44]				
Biological vulnerabilities					
HIV & alcohol use		−0.07 [−0.19, 0.1]	−0.03 [−0.11, 0.03]	0.94 [0.83, 1.07]	0.86 [0.81, 0.91]
Effect of HIV among non-alcohol users (A+ | B−)	1.86 [1.62, 2.13]				
Effect of alcohol use among non–HIV (B+ | A−)	1.31 [1.2, 1.42]				
Effect of HIV among alcohol users (A+ | B+)	1.6 [1.39, 1.85]				
Effect of alcohol use among HIV (B+ | A+)	1.13 [1.02, 1.25]				
Combined HIV & alcohol Use (A+ & B+)	2.09 [1.78, 2.47]				
HIV & tobacco use		0.14 [0.01, 0.34]	0.06 [−0.01, 0.11]	1.12 [1.01, 1.25]	0.94 [0.89, 1]
Effect of HIV among non-tobacco users (A+ | B−)	1.86 [1.62, 2.13]				
Effect of tobacco use among non–HIV (B+ | A−)	1.33 [1.24, 1.44]				
Effect of HIV among tobacco users (A+ | B+)	1.75 [1.52, 2.02]				
Effect of tobacco use among HIV (B+ | A+)	1.26 [1.15, 1.38]				
Combined HIV & tobacco Use (A+ & B+)	2.33 [1.99, 2.74]				
HIV & drug use		**1.98 [1.39, 2.76]**	**0.33 [0.26, 0.38]**	**1.64 [1.48, 1.82]**	**1.01 [0.96, 1.07]**
Effect of HIV among non-drug users (A+ | B−)	1.86 [1.62, 2.13]				
Effect of drug use among non–HIV (B+ | A−)	3.21 [2.9, 3.56]				
Effect of HIV among drug users (A+ | B+)	1.88 [1.63, 2.18]				
Effect of drug use among HIV (B+ | A+)	3.26 [2.91, 3.65]				
Combined HIV & drug use (A+ & B+)	6.05 [5.12, 7.15]				
HIV & not diabetes		−0.13 [−0.4, 0.1]	−0.07 [−0.21, 0.05]	0.88 [0.7, 1.11]	0.86 [0.75, 0.98]
Effect of HIV among diabetes (A+ | B−)	1.86 [1.62, 2.13]				
Effect of not diabetes among non–HIV (B+ | A−)	1.23 [1.19, 1.28]				
Effect of HIV among not diabetes (A+ | B+)	1.59 [1.54, 1.63]				
Effect of not diabetes among HIV (B+ | A+)	1.05 [0.92, 1.21]				
Combined HIV & not diabetes (A+ & B+)	1.96 [1.87, 2.05]				
Not diabetes & drug use		**−0.62 [−0.96, −0.31]**	**−0.22 [−0.34, −0.11]**	**0.75 [0.65, 0.86]**	**0.71 [0.65, 0.79]**
Effect of not diabetes among non-drug users (A+ | B−)	1.23 [1.19, 1.28]				
Effect of drug use among diabetes (B+ | A−)	3.21 [2.9, 3.56]				
Effect of not diabetes among drug users (A+ | B+)	0.88 [0.79, 0.98]				
Effect of drug use among not diabetes (B+ | A+)	2.3 [2.23, 2.37]				
Combined not diabetes & drug use (A+ & B+)	2.83 [2.7, 2.97]				
Not diabetes & tobacco use		0.1 [0, 0.19]	0.06 [0, 0.12]	1.17 [0.98, 1.4]	1.01 [0.94, 1.09]
Effect of not diabetes among non-tobacco users (A+ | B−)	1.23 [1.19, 1.28]				
Effect of tobacco use among diabetes (B+ | A−)	1.33 [1.24, 1.44]				
Effect of not diabetes among tobacco users (A+ | B+)	1.25 [1.16, 1.34]				
Effect of tobacco use among not diabetes (B+ | A+)	1.35 [1.32, 1.38]				
Combined not diabetes & tobacco use (A+ & B+)	1.67 [1.59, 1.74]				

(Table 4 continues on next page)

LTFU outcome

Interactions	Odds ratio [95% CI]	RERI	AP	SI	Multiplicative scale
(Continued from previous page)					
Not diabetes & alcohol use		**0.29 [0.17, 0.4]**	**0.16 [0.1, 0.22]**	**1.54 [1.25, 1.88]**	**1.14 [1.04, 1.23]**
Effect of not diabetes among non-alcohol users (A+ | B−)	1.23 [1.19, 1.28]				
Effect of alcohol use among diabetes (B+ | A−)	1.31 [1.2, 1.42]				
Effect of not diabetes among alcohol users (A+ | B+)	1.48 [1.44, 1.53]				
Effect of alcohol use among not diabetes (B+ | A+)	1.4 [1.29, 1.52]				
Combined not diabetes & alcohol use (A+ & B+)	1.83 [1.74, 1.92]				
Pregnancy & retreatment		0.47 [−1.91, 7.63]	0.19 [−1.71, 0.97]	1.45 [0.79, 2.68]	1.1 [0.91, 1.34]
Effect of pregnancy among new cases (A+ | B−)	1.33 [0.32, 5.56]				
Effect of retreatment among non-pregnancy (B+ | A−)	1.7 [1.33, 2.16]				
Effect of pregnancy among retreatment (A+ | B+)	1.47 [0.35, 6.19]				
Effect of retreatment among pregnancy (B+ | A+)	1.87 [1.37, 2.55]				
Combined pregnancy & retreatment (A+ & B+)	2.5 [0.58, 10.71]				

This table presents results from an interaction analysis assessing how overlapping vulnerabilities (e.g., tobacco use, alcohol use, homelessness, pregnancy, HIV) jointly influence the likelihood of composite unfavorable outcomes. Each main row shows the overall interaction measure (Odds Ratio [95% CI]) plus four interaction metrics: RERI (Relative Excess Risk due to Interaction), AP (Attributable Proportion), SI (Synergy Index), and a measure on the multiplicative scale. Subsequent rows detail the effect of each vulnerability alone (when the other vulnerability is absent). RERI and AP values above zero indicate positive interaction (synergy) on the additive scale, whereas SI and multiplicative measures above 1 indicate positive interaction (synergy) on the multiplicative scale. Values below these thresholds indicate antagonism.

Table 4: **Interaction effects of overlapping vulnerabilities on ATT loss to follow-up.**

Each vulnerability group demonstrated distinct patterns of risk for unfavorable outcomes. The strongest predictors were homelessness, HIV infection, and drug use, whereas incarceration and healthcare work were unexpectedly associated with better outcomes. Across all groups, LTFU emerged as the most frequent unfavorable outcome, followed by death. Treatment interruption in these populations remains a major barrier to TB control in Brazil, fueling ongoing transmission and posing a critical obstacle to achieving TB elimination goals.

Our findings confirm that ATT outcomes are shaped by both social and biological vulnerabilities, though through distinct mechanisms. Social vulnerabilities, such as homelessness, incarceration, immigration, healthcare work, drug and alcohol use, tobacco use, pregnancy, and retreatment history, were mainly associated with barriers to care, poor adherence, and higher risks of LTFU or death. In contrast, biological vulnerabilities, including HIV infection and TB-DM, may affect not only disease progression and treatment response but also clinical presentation, which is often atypical and can delay timely diagnosis and initiation of care.

When social and biological vulnerabilities co-occurred, their combined effect was frequently greater than the sum of their independent contributions, emphasizing the need for integrated responses that simultaneously address structural determinants and biomedical risks. Although, these findings also demonstrated a high degree of heterogeneity, with several pairs were sub-multiplicative or null on the multiplicative scale (ME $\leq$ 1).

Interactions among vulnerabilities revealed complex dynamics and heterogeneous interactions. The most striking example was the synergistic additive interaction between HIV infection and drug use, which substantially increased the risk of both death and LTFU. These findings support Maciel et al.'s framework for TB determinants in Brazil,[21] and with studies in other high-burden countries that show HIV and substance use jointly amplify TB mortality and treatment discontinuation.[28,29]

Some interactions showed protective or antagonistic effects. Incarceration, for example, was consistently associated with lower risk of unfavourable outcomes, particularly among hard-to-reach groups like immigrants and retreatment cases. This pattern likely reflects the controlled environment during incarceration, where structured follow-up and DOT coverage can increase the probability of ATT completion.[21,30,31] However, this protection may not extend to individuals released before completing ATT, since continuity of care and traceability across community health services are often limited. Such interruptions represent a potential gap in the TB care cascade for this population. While additional protective mechanisms may exist, these results support expanding DOT and strengthening continuity-of-care models both in custodial and community settings.[30,32]

Not all combined vulnerabilities were associated with additional additive risk. For example, homelessness did not appear to amplify risk when combined with other factors on the additive scale, although in some pairs (ex. homelessness with retreatment) we observed multiplicative antagonism. This may reflect the already high baseline vulnerability in this population. The frequent overlap of substance use and, mental illness, and other social disadvantages suggests that

homelessness often represents a cluster of coexisting risks rather than a single isolated factor, which could explain the consistently elevated LTFU observed here and in prior studies.[33,34] Nevertheless, this finding should be interpreted with caution, as limitations in surveillance data and potential misclassification may underestimate the compounded effects of homelessness when it co-occurs with other vulnerabilities.

TB-DM comorbidity showed a distinct pattern: lower loss to follow-up yet higher mortality. This may reflect increased contact with health services through diabetes care, which facilitates monitoring, but at the same time greater biological susceptibility to severe TB disease that raises the risk of death.[12,35,36] It is important to note, however, that the diabetes variable in SINAN is self-reported. Patients who know they are diabetic are more likely to be already engaged with the health system, and the database lacks details on diabetes type, treatment, duration of diagnosis, and other potential confounders. These limitations must be considered when interpreting the observed associations.

Pregnancy was also associated with poorer outcomes, a finding that contrasts with expectations given the existence of targeted public health programs and antenatal care policies in Brazil.[37] In our study, the high rates of loss to follow-up among pregnant women suggest persistent gaps in continuity of care during pregnancy, pointing to vulnerabilities that are not fully addressed by current strategies. These findings underscore the need for systematic collection of detailed pregnancy-related data in TB surveillance systems, including gestational age, maternal comorbidities, and ATT history, as well as for specialized clinical attention for this population. From a biological perspective, pregnancy is known to modulate immune responses, which may increase susceptibility to infectious diseases such as TB.[38,39] At the same time, our results suggest that pregnancy also has a social dimension in the context of TB, as evidenced by the elevated risk of non-adherence and loss to follow-up, highlighting barriers that go beyond the biological risk of disease progression already established in the literature.

Contrary to previous literature, our analysis found that HCW status was protective against unfavorable TB outcomes in Brazil, despite high occupational exposure risk.[9] This apparent protective effect should be interpreted with caution, as it may reflect factors not captured in the surveillance system, such as earlier access to diagnostic services, better health literacy, and greater treatment engagement among HCWs. It is also possible that reporting bias or unmeasured confounding contributed to these findings, since HCWs are more likely to be tested and followed within structured health services. These results highlight the need for further studies that specifically address occupational TB in Brazil, exploring both clinical outcomes and systemic factors that may facilitate better adherence in this group, while also recognizing that in many low- and middle-income countries HCWs remain at high risk for poor outcomes due to limited resources.

Abandoning ATT increases TB transmission and drug resistance.[40] and the high rates of LTFU observed among Brazil's vulnerable populations illustrate how fragile treatment continuity can be. Within this context, DOT has consistently emerged as a protective strategy across diverse groups, reinforcing its central role in TB control.[41–43] Among people experiencing homelessness, for example, a previous study found that those receiving DOT were around 40% more likely to complete treatment compared with those on self-administered therapy[44] underscoring the program's potential to improve adherence in hard-to-reach groups. In custodial settings, the structured environment may also facilitate monitoring and follow-up.[21,30,31] but this protection may be lost when individuals are released before completing treatment, given the limited mechanisms to ensure continuity of care across health services. Importantly, DOT should not be interpreted as a stand-alone solution: evidence from other countries demonstrates that patient-centered approaches integrated with social support interventions, such as food packages, housing assistance, or financial incentives, are effective in improving adherence and ATT completion, and similar models could be considered in Brazil as complementary strategies to DOT.[45] Taken together, these considerations highlight that DOT works best when embedded within broader, context-sensitive strategies that address both biomedical and social determinants of TB.[25,27]

Our findings reveal heterogeneous vulnerability profiles and effect modification when risks intersect with some superadditive interactions being accompanied by antagonistic or null multiplicative interactions. HIV was the strongest predictor of death, especially when combined with substance use, consistent with prior SINAN-based studies.[40,46] Homelessness was the main risk factor for LTFU, likely reflecting multiple coexisting vulnerabilities. These results emphasize that vulnerabilities rarely act in isolation, but rather interact to create compounded risks, underscoring the need for integrated and multidisciplinary approaches that combine biomedical care with targeted social support to improve TB outcomes. Nonetheless, interaction is a scale-dependent measurement, therefore interpretation should be dependent on the chosen scale.

This study has limitations. Analyses relied on secondary surveillance data from SINAN, which is subject to underreporting, misclassification, and missing information. Some vulnerabilities were recorded with limited precision, for example, diabetes was self-reported without details on type, treatment, or disease duration, and pregnancy was registered as a binary variable without gestational age or maternal comorbidities. These constraints limit the depth of

interpretation and may have introduced residual confounding. Moreover, certain combinations of vulnerabilities were rare, restricting the precision of interaction estimates. Finally, results from additive and multiplicative scales did not always align, an expected phenomenon that reflects the inherent scale-dependence of interaction assessment. Moreover, the small number of cases with certain overlapping vulnerabilities, such as TB-DM combined with tobacco use, reduced the statistical power to explore these interactions in depth and limited the calculation of some complementary measures, including the SI. Despite these limitations, our analysis of a comprehensive and validated national registry in a high TB burden setting identified key vulnerabilities associated with poor ATT outcomes, particularly homelessness, HIV, drug use, and pregnancy, and demonstrated that overlapping vulnerabilities, especially when social and biological factors intersect, substantially increase the risk of unfavorable outcomes.

LTFU was the most frequent unfavorable outcome across all vulnerable groups, reinforcing the urgency of retention-focused strategies. Public health efforts in Brazil should prioritize patient-centred DOT, integrate TB-HIV and TB-DM services, and link social supports to mitigate structural barriers. Multisectoral approaches, combining clinical integration with social protection, are essential to reduce inequities and improve outcomes among people facing overlapping vulnerabilities.

Contributors

Conceptualization, B.B-D., K.V.S., M.M.R and B.B.A.; Data verification and curation, B.B-D., K.V.S., M.M.R, M.A-P., A.T.L.Q. and B.B.A.; Investigation, B.B-D, K.V.S., J.P.M-P; M.M.R, M.C.S., B.N., A.L.K., L.M.; P.F.R.; V.C.R., T.R.S., M.C.S., and B.B.A.; Formal analysis, B.B-D., M.M.R., and B.B.A.; Funding acquisition, A.L.K., V.C.R., T.R.S., M.C.S., M.M.R., and B.B.A.; Methodology, B.B-D., K.V.S., M.M.R., and B.B.A.; Project administration, M.M.R., M.C.F., T.R.S., and B.B.A.; Resources, B.B.-D., T.R.S., and B.B.A.; Software, B.B-D., M.M.R, M.A-P., and B.B.A.; Supervision, M.M.R., and B.B.A.; Writing—original draft, B.B-D., K.V.S., M.M.R., and B.B.A.; Writing—review and editing, all authors.

Data sharing statement

The data that support the findings of this study will be available upon reasonable request to the corresponding author of the study.

Statement on the use of AI tools

No AI tools were used in the preparation or analysis of this work.

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. All other authors declare no competing interests.

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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.2025.101305.

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