Cost-effectiveness and health impact of screening and treatment of *Mycobacterium tuberculosis* infection among formerly incarcerated individuals in Brazil: a Markov modelling study

Ana van Lieshout Titan, Fayette Klaassen, Daniele Maria Pelissari, José Nildo de Barros Silva Júnior, Kleydson Alves, Layana Costa Alves, Mauro Sanchez, Patricia Bartholomay, Fernanda Dockhorn Costa Johansen, Julio Croda, Jason R Andrews, Marcia C Castro, Ted Cohen, Cornelis Vuik, Nicolas A Menzies

Summary

Background Individuals who were formerly incarcerated have high tuberculosis incidence, but are generally not considered among the risk groups eligible for tuberculosis prevention. We investigated the potential health impact and cost-effectiveness of *Mycobacterium tuberculosis* infection screening and tuberculosis preventive treatment (TPT) for individuals who were formerly incarcerated in Brazil.

Methods Using published evidence for Brazil, we constructed a Markov state transition model estimating tuberculosis-related health outcomes and costs among individuals who were formerly incarcerated, by simulating transitions between health states over time. The analysis compared tuberculosis infection screening and TPT, to no screening, considering a combination of *M tuberculosis* infection tests and TPT regimens. We quantified health effects as reductions in tuberculosis cases, tuberculosis deaths, and disability-adjusted life-years (DALYs). We assessed costs from a tuberculosis programme perspective. We report intervention cost-effectiveness as the incremental costs per DALY averted, and tested how results changed across subgroups of the target population.

Findings Compared with no intervention, an intervention incorporating tuberculin skin testing and treatment with 3 months of isoniazid and rifapentine would avert 31 (95% uncertainty interval 14–56) lifetime tuberculosis cases and 4·1 (1·4–5·8) lifetime tuberculosis deaths per 1000 individuals, and cost US$242 per DALY averted. All test and regimen combinations were cost-effective compared with no screening. Younger age, longer incarceration, and more recent prison release were each associated with significantly greater health benefits and more favourable cost-effectiveness ratios, although the intervention was cost-effective for all subgroups examined.

Interpretation *M tuberculosis* infection screening and TPT for individuals who were formerly incarcerated appears cost-effective, and would provide valuable health gains.

Funding National Institutes of Health.

Lancet Glob Health 2024; 12: e1446–55

For the Portuguese translation of the abstract see Online for appendix 1

Department of Global Health and Population (A van Lieshout Titan BSc, F Klaassen PhD, Prof M C Castro PhD, N A Menzies PhD) **and Center for Health Decision Science** (N A Menzies), **Harvard T H Chan School of Public Health, Boston, MA, USA; Delft Institute of Applied Mathematics, Delft University of Technology, Delft, Netherlands** (A van Lieshout Titan, Prof C Vuik PhD); **National Tuberculosis Programme** (D M Pelissari PhD, J N de Barros Silva Júnior MSc, K Alves PhD, L C Alves MSc, F D C Johansen MSc) **and Health and Environment Surveillance Secretariat** (Prof M Sanchez PhD, P Bartholomay PhD), **Ministry of Health, Brasilia, Brazil; Collective Health Institute, Federal University of Bahia, Salvador, Bahia, Brazil** (L C Alves); **Universidade Federal de Mato Grosso do Sul, Campo Grande, Brazil** (J Croda PhD); **Fiocruz Mato Grosso do Sul, Fundação Oswaldo Cruz, Campo Grande, Brazil** (J Croda); **Department of Epidemiology of Microbial Diseases, Yale School of Public Health, New Haven, CT, USA** (Prof T Cohen PhD); **Division of Infectious Diseases and Geographic Medicine, Stanford University, Stanford, CA, USA** (Prof J R Andrews PhD)

Introduction

In many countries, prisons are high-risk locations for transmission of *Mycobacterium tuberculosis* and might create additional risks of *M tuberculosis* infection for individuals in surrounding communities.[1,2] Prisons serve as amplifiers of tuberculosis transmission for several reasons. Living arrangements within prisons are often overcrowded and poorly ventilated, increasing opportunities for transmission between individuals who are infectious and those susceptible to infection.[1,3] Individuals entering prisons might have a higher prevalence of infectious tuberculosis disease than the general population, because of the shared socioeconomic determinants of tuberculosis and incarceration. Compared with the general community, incarcerated individuals might also have a higher prevalence of risk factors for rapid tuberculosis progression, including undernutrition, untreated comorbid health conditions, smoking, and use of illicit drugs. Finally, in settings in which prison health services are scarce, individuals who are infectious might experience greater delays before initiating tuberculosis treatment, extending the duration of infectiousness. As a result, high *M tuberculosis* infection and tuberculosis disease incidence among incarcerated populations have been documented in many countries.[4,5]

Prison-based tuberculosis transmission is a particular challenge for countries in the Americas.[6] In Brazil, the tuberculosis notification rate among individuals who are incarcerated is estimated to be 40 times greater than in the non-incarcerated population, with this difference widening between 2010 and 2019.[7] Combined with a growing prison population, total cases among

Correspondence to:
Ana van Lieshout Titan, Department of Global Health and Population, Harvard T H Chan School of Public Health, Boston, MA 02115, USA
anavanlieshouttitan23@gmail.com

Research in context

Evidence before this study

We reviewed documents from WHO and the Brazilian Ministry of Health, and searched PubMed on Nov 21, 2023 using the MesH advanced search engine with no date or language restrictions. We used the search terms "latent tuberculosis", "tuberculosis infection", or "*M tuberculosis* infection" and "prisoners", "ex prisoners", "formerly incarcerated", or "incarcerated" and "TPT", "preventive therapy", or"tuberculosis preventive therapy". We found several studies analysing the correlation between tuberculosis and prisons, but no other cost-effectiveness analysis studies of screening and treatment for *Mycobacterium tuberculosis* infection for individuals who were formerly incarcerated. In many settings, individuals who are incarcerated have been shown to face higher risks of *M tuberculosis* infection than the general population. Individuals exiting prison have been found to have elevated tuberculosis incidence up to 7 years after release, and studies have also reported evidence of elevated tuberculosis incidence in surrounding communities. Although several studies have investigated the health impact and cost-effectiveness of interventions to detect and prevent tuberculosis disease within prisons, few studies have examined the health impact and cost-effectiveness of interventions to treat *M tuberculosis* infection among individuals who were formerly incarcerated.

Added value of this study

Using a Markov model, we simulated lifetime results, including tuberculosis cases, tuberculosis deaths, and life-years spent with tuberculosis among a cohort of individuals who were formerly incarcerated in Brazil and offered screening and treatment for *M tuberculosis* infection. To our knowledge, this study is the first to investigate the health impact and cost-effectiveness of screening and treatment among this cohort. The results contribute to the ongoing efforts to effectively reduce the tuberculosis burden and reach the WHO End Tuberculosis goals by 2030.

Implications of all the available evidence

Screening and treatment of *M tuberculosis* infection among individuals who were formerly incarcerated would produce substantial health benefits and be highly cost-effective in the setting examined in this study.

individuals who are incarcerated increased by 40% between 2015 and 2022.[8,9]

In addition to high incidence within prisons, prison-based tuberculosis transmission will also lead to many individuals exiting prison with recent *M tuberculosis* infection. Although data on tuberculosis incidence among individuals who were formerly incarcerated are scarce, evidence suggests that they have elevated tuberculosis incidence compared with the general population.[10] The short duration of incarceration for most prisoners, combined with the comparatively long incubation period for tuberculosis, means that many individuals will be at risk of progressing to tuberculosis disease after prison release.[4,11] These factors could contribute to elevated tuberculosis incidence among individuals who were formerly incarcerated. Within Brazil, elevated tuberculosis incidence among this group has been documented up to 7 years after release,[1] representing an ongoing health risk for these individuals and contributing to ongoing transmission in their communities.[10]

The time between *M tuberculosis* infection and the development of tuberculosis disease represents an opportunity for prevention. Brazil has adopted the WHO End Tuberculosis strategy, which provides a roadmap for accelerating global reductions in tuberculosis incidence and mortality, and has committed to eliminating tuberculosis by 2030.[12,13] Expanding access to tuberculosis preventive treatment (TPT) for populations at high risk of disease is a key component of the WHO End Tuberculosis strategy, and treating *M tuberculosis* infection among individuals who were formerly incarcerated could reduce tuberculosis burden in this marginalised group and limit the effect of prison-based tuberculosis transmission on affected communities.[14] Previous research has shown the limited effect of mass screening for tuberculosis disease within prisons and prompted calls for the investigation of other potential control measures, such as preventive screening and treatment.[15,16]

In this study, we investigated the potential health impact and cost-effectiveness of a tuberculosis prevention intervention among individuals who were formerly incarcerated, as compared to a base-case scenario representing no *M tuberculosis* infection screening and passive tuberculosis diagnosis. We examine the relative performance of different combinations of *M tuberculosis* infection test and regimen type and report how the effect of an intervention varies as a function of age at testing, duration of incarceration, and delay between prison release and testing.

Methods

Study model

We constructed a Markov state transition model simulating future health outcomes and intervention-related costs among a cohort of individuals who were formerly incarcerated.[17] In this model, the study cohort is divided into compartments representing differences in tuberculosis health state and the receipt of treatment for *M tuberculosis* infection and tuberculosis disease (figure 1A). The model tracks individuals transitioning between these health states as a result of disease natural history and the initiation and discontinuation of treatment and records deaths from tuberculosis or non-tuberculosis causes. The model was implemented as

a set of difference equations evaluated with 1-month timesteps and used to simulate disease transitions, costs, and health outcomes for the study cohort over their remaining life course. Upon initial infection, individuals enter one of several *M tuberculosis* infection compartments designed to reproduce empirical trends in tuberculosis progression rates over time since infection.[4,18–22] Individuals progressing to untreated tuberculosis disease can either be diagnosed and initiate tuberculosis treatment, spontaneous cure (ie, control the disease without treatment), or die, either from tuberculosis or background causes.[23] Individuals treated for tuberculosis disease were assumed to receive a standardised 6-month treatment, following national guidelines.[18] Individuals who recover from tuberculosis disease (by treatment or self-cure) face risks of reinfection, recurrent tuberculosis disease, or death because of background causes. Reinfection is represented as a monthly risk of infection applied to all previously infected individuals without current tuberculosis disease. We assumed that these individuals would have partial immunity compared to unexposed individuals.[21] Background mortality was based on general population life tables for Brazil.[24]

Intervention scenarios

We constructed intervention scenarios representing a one-time screening for *M tuberculosis* infection for individuals in the study cohort (figure 1B). We modelled *M tuberculosis* infection screening and treatment following WHO recommendations,[25] with individuals who accept screening being tested for *M tuberculosis* infection, and individuals testing positive subsequently screened for tuberculosis disease.[26] We assumed that individuals diagnosed with *M tuberculosis* infection but without tuberculosis disease would be offered TPT following a WHO-approved regimen. We included a probability of refusal of TPT. We assumed a fraction of individuals would discontinue TPT before completing the regimen, and included a probability of cure with partial treatment. We assumed that a fraction of those completing the regimen would clear *M tuberculosis* infection. Cured individuals were assumed to face no further tuberculosis risk from their original infection, but could be reinfected. TPT was also assumed to confer protection against *M tuberculosis* infection and progression to tuberculosis disease while individuals were receiving the regimen. Individuals diagnosed with tuberculosis disease were assumed to initiate tuberculosis disease treatment following national protocols.[27] Individuals testing negative for *M tuberculosis* infection were assumed to receive no further screening or treatment. We assumed the intervention would be offered to all individuals in the cohort except those being treated for tuberculosis disease. In addition to these intervention scenarios, we constructed a base-case scenario that assumed there would be no screening for *M tuberculosis* infection. For all strategies, we assumed tuberculosis disease arising in the future would be identified and treated via passive diagnosis. We did not consider the possible changes to the health gains and costs associated with the reduction of transmission by individuals in the study cohort.

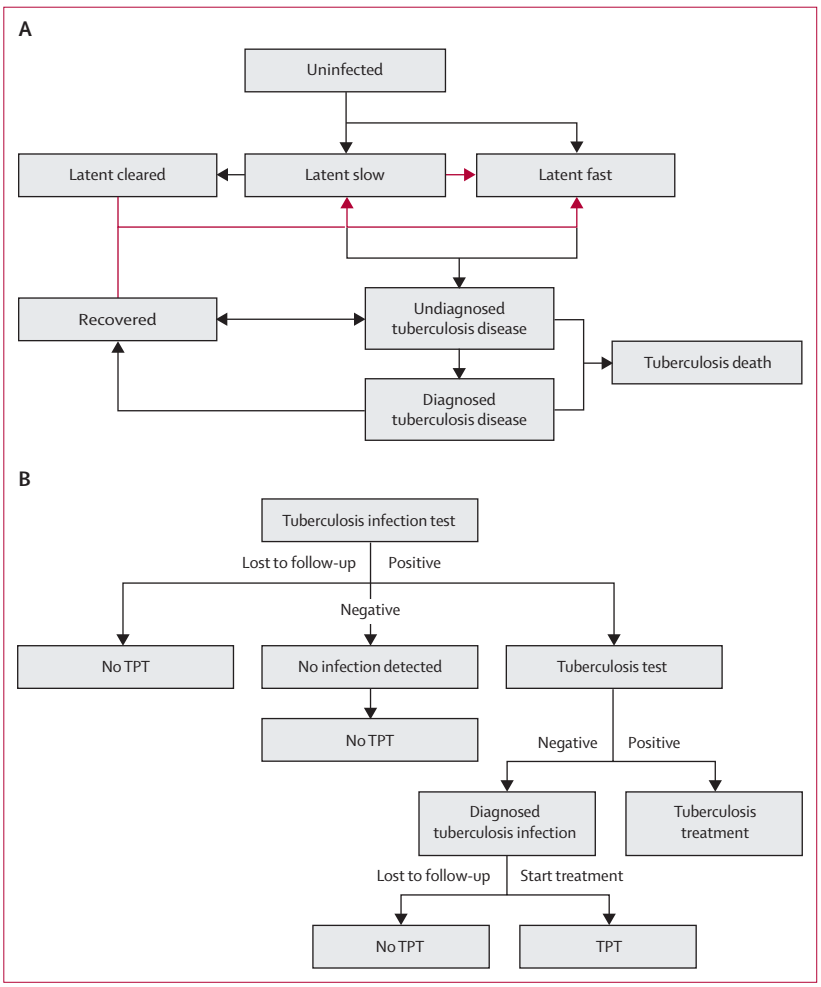

Figure 1: **Compartments and transitions of the Markov model (A) and decision tree for *Mycobacterium tuberculosis* infection screening and treatment (B)**
Red arrows depict reinfection and black arrows depict disease natural history and continuation or discontinuation of treatment. All health states are subject to non-tuberculosis mortality. TPT=tuberculosis preventive treatment.

For the intervention scenarios, we considered two different tests for *M tuberculosis* infection (the tuberculin skin test [TST] and interferon gamma release assays [IGRA]),[25] and four TPT regimens (1 month of isoniazid and rifapentine [1HP] every day, 3 months of isoniazid and rifapentine [3HP] every week, 4 months of rifampicin [4R] every day, and 9 months of isoniazid [9H] every day).[26] We considered each combination of test and regimen.

Model parametrisation

Parameters describing tuberculosis epidemiology and natural history were estimated using a Bayesian evidence

synthesis approach,[28] with prior distributions for each parameter defined on the basis of published values, and calibrated to reproduce available evidence on tuberculosis risks associated with incarceration. We validated the fitted model against published standards for tuberculosis natural history models.[29] We used the RStan package (version 2.21.8) to estimate epidemiological parameters (fitted values for these parameters are provided in table 1 and additional details in appendix 2 p 2). Parameters defining test sensitivity and specificity, regimen efficacy and discontinuation rates, and costs for each intervention component were based on published studies (table 1).

See Online for appendix 2

	Value (95% uncertainty interval)	Source
Test and TPT parameters		
Probability of return for *Mycobacterium tuberculosis* infection test results	0·88 (0·65–0·97)	Steffen et al[30]
Probability of starting TPT, if indicated	0·82 (0·74–0·97)	Steffen et al[30]
Sensitivity of TST (induration ≥10 mm)	0·84 (0·82–0·85)	Doan et al[31]
Specificity of TST (induration ≥10 mm)	0·79 (0·76–0·82)	Doan et al[31]
Sensitivity of IGRA (QFT–GIT)	0·88 (0·80–0·94)	Zhang et al[32]
Specificity of IGRA (QFT–GIT)	0·99 (0·97–0·99)	Zhang et al[32]
Specificity of initial tuberculosis disease screening	0·70 (0·60–0·80)	WHO[33]
Efficacy of 9H regimen	0·80 (0·65–0·93)	Zenner et al[34] and IUATCP[35]
Efficacy of 4R regimen	0·80 (0·65–0·93)	Sterling et al[36]
Efficacy of 3HP regimen	0·80 (0·65–0·93)	Sterling et al[36]
Efficacy of 1HP regimen	0·80 (0·65–0·93)	Swindells et al[37]
Probability of discontinuing TPT, in first month of TPT	0·10 (0·05–0·15)	Araújo et al[38]
Probability of discontinuing TPT, subsequent months	0·03 (0·02–0·05)	Araújo et al[38]
Probability of cure after fulfilling half of TPT	0·50 (0·10–0·90)	Assumed
Disease progression parameters*		
Rate of *M tuberculosis* infection for individuals currently incarcerated	0·0043 (0·0026–0·0064)	Estimated
Rate ratio of *M tuberculosis* infection for individuals currently incarcerated	103 (64–156)	Estimated
Fraction of individuals who were infectious transitioning to latent–fast state	0·11 (0·08–0·14)	Estimated
Tuberculosis progression for latent fast state	1·33 (0·96–1·80)	Estimated
Tuberculosis progression for latent slow state	0·0049 (0·0022–0·0085)	Estimated
Rate of progression from latent slow-to-cleared state	0·049 (0·028–0·076)	Estimated
Rate ratio of infection for individuals with previous infection	0·22 (0·17–0·27)	Estimated
Tuberculosis diagnosis rate	2·30 (1·8–2·8)	Estimated
Tuberculosis-specific mortality	0·13 (0·06–0·23)	Estimated
Self-recovery rate	0·13 (0·06–0·23)	Estimated
Tuberculosis treatment completion rate	2	Ministério da Saúde[18]
Costs (2022 US dollars)†		
Cost of tuberculosis disease diagnosis	54·34 (27·17–108·68)	Nsengiyumva[39]
Monthly cost of tuberculosis disease treatment	144 (108–180)	Nsengiyumva[39]
Monthly cost of 9H *M tuberculosis* infection regimen	4·91 (2·46–7·37)	Bastos et al[40] and Ministério da Saúde[41]
Monthly cost of 4R *M tuberculosis* infection regimen	9·02 (4·51–13·53)	Bastos et al[40] and Ministério da Saúde[41]
Monthly cost of 3HP *M tuberculosis* infection regimen	11·68 (5·84–17·52)	Bastos et al[40] and Ministério da Saúde[41]
Monthly cost of 1HP *M tuberculosis* infection regimen	58·99 (29·50–88·49)	Bastos et al[40] and Ministério da Saúde[41]
Costs of IGRA	38·44 (31·31–46·98)	Loureiro et al[42]
Costs of TST	8·20 (4·10–16·41)	Steffen et al[43]
Costs of chest x-ray	6·28 (3·98–8·53)	Loureiro et al[42] and Santos et al[44]

(Table 1 continues on next page)

Study outcomes

We quantified health benefits as reductions in tuberculosis-attributable disability-adjusted life-years (DALYs), comparing each intervention scenario to the base case. We also calculated the number of tuberculosis cases and tuberculosis deaths averted. We reported DALYs, tuberculosis cases, and tuberculosis deaths per 1000 people. We estimated incremental costs in 2022 US dollars from a tuberculosis programme perspective, on the basis of changes in diagnosis and treatment costs between intervention scenarios and the base case. We estimated all outcomes over the lifetime of the study cohort.

We estimated incremental cost-effectiveness ratios (ICERs) to describe the cost-effectiveness of each intervention approach. Cost-effectiveness results are reported as the incremental cost per DALY averted, with costs and health outcomes discounted using a 3% discount rate.[46] In sensitivity analyses, we re-estimated ICERs with the undiscounted costs and health outcomes (appendix 2 p 8). An intervention was deemed cost-effective in comparison to another intervention if the ICER was lower than the local cost-effectiveness threshold. This threshold was defined as 71–109% of current gross domestic product (GDP) per capita, on the basis of estimates of the opportunity cost of health-care spending.[47] This implied a threshold within the range of US$6300–9700 per DALY averted, on the basis of a 2022 Brazilian GDP per capita of $8917.[48] Interventions were dominated if they had higher costs and worse health outcomes than other available strategies. Uncertainty in the ICERs was taken into account in the cost-effectiveness acceptability curves (CEACs). We did all analyses in R (V4.2.3).

Analysis of age, duration of incarceration, and delay between release, and testing

For the main analysis, we assumed that the cohort offered screening would be age 30 years, have completed 2 years in prison, and would have been released from prison 3 months before the intervention was offered. We did additional analyses to understand how each of these factors (age at screening, duration of incarceration, and delay between release and testing) would affect intervention health impact and cost-effectiveness. To do so, we adjusted each factor over a range of plausible values (holding the other two factors at their original values) and recalculated study results.

We varied age at screening between ages 25 years and 65 years, duration of incarceration between 1 month and 10 years, and delay between release and testing from 0 months to 10 years (appendix 2 p 5). These ranges were selected to broadly represent the variation in these characteristics within the target population.

Statistical analysis

We propagated uncertainty through the analysis using second-order Monte Carlo simulation.[49] We specified probability distributions for each uncertain parameter (table 1) and used these distributions to sample 1000 values for each parameter. Using the Markov model, we recalculated study outcomes for each of these parameter sets, yielding a distribution of results for each outcome. We summarised these distributions as the mean and 95% uncertainty interval, representing the uncertainty in each study outcome because of the combined uncertainty in model parameters.

Sensitivity analyses

We did one-way deterministic sensitivity analyses testing how changes in each parameter affected cost-effectiveness results. To do so, we recalculated results from the Markov model while varying each parameter between the ranges (table 1), holding other parameters at their mean value. We did an additional sensitivity analysis to understand how elevated future reinfection rates (as could happen with reincarceration) change cost-effectiveness results. To do so, we specified an elevated value for the tuberculosis force of infection after prison release, operationalised as a rate ratio applied to the force of infection in the general population, and varied this rate ratio between 2 and 50. This rate ratio was assumed to decline linearly to 1 over the 20 years after release, to represent a declining probability of reincarceration with greater time since release (appendix 2 p 7). We also calculated CEACs[50] to report how the probability of each strategy being cost-effective changed across the range of the cost-effectiveness threshold.

Role of the funding source

The funding source had no role in the study design, data analysis, data interpretation, or writing of this report.

Results

As estimated by the Bayesian evidence synthesis, 2·4% (95% uncertainty interval 1·8–3·1) of the starting cohort was estimated to have tuberculosis disease and 57·1% (42·5–73·3) to have *M tuberculosis* infection (appendix 2 p 3).

Under the base-case scenario (no screening and TPT), we estimated there would be 120 (95% uncertainty interval 75–181) tuberculosis disease cases, 13 (5–25) tuberculosis deaths, and 432 (186–772) DALYs per 1000 people (undiscounted) when estimated over the lifetime of individuals in the study cohort. Each of these outcomes was reduced under the interventions scenarios, with health impact ranging from 28 (13–52) tuberculosis cases, 3·7 (1·3–7·7) tuberculosis deaths, and 126 (49–246) tuberculosis DALYs averted per 1000 people under the TST and 9H scenario, up to 34 (16–62) tuberculosis cases, 4·5 (1·5–9·4) tuberculosis deaths, and 149 (55–292) tuberculosis DALYs averted under the IGRA and 1HP scenario (a 28%, 95% uncertainty interval 18–38 reduction in lifetime tuberculosis cases; 33%, 22–43 reduction in deaths; and 30%, 6–49 reduction in DALYs compared with the base case). In general, greater health gains were produced under scenarios using IGRA than TST, and with shorter TPT regimens instead of longer regimens (table 2).

Undiscounted lifetime costs were $99 585 (58 552–157 598) per 1000 people under the base-case scenario. Costs were higher under the intervention scenarios, with incremental costs (compared with the base case) ranging from $8790 (–14 213 to 28 079) for the TST and 3HP scenario and up to $44 402 (15 597 to 69 099) for the IGRA and 1HP scenario. Incremental costs were higher for scenarios using IGRA rather than TST, and using 9H and 1HP as the TPT regimen versus 3HP or 4R (table 2).

	Value (95% uncertainty interval)	Source
(Continued from previous page)		
Other parameters		
Disability weight for tuberculosis disease	0·333 (0·224–0·454)	Salomon et al[45]
Discount rate	0·03	Wilkinson et al[46]

1HP=1 month of isoniazid and rifapentine every day. 3HP=3 months of isoniazid and rifapentine every week. 4R=4 months of rifampicin every day. 9H=9 months of isoniazid every day. All rates shown are annual rates. IGRA=interferon gamma release assays. TPT=tuberculosis preventive treatment. TST=tuberculin skin test. QFT-GIT=QuantiFERON-TB Gold In-Tube. *Estimated parameters were derived by fitting previous model evidence on tuberculosis natural history, via Bayesian evidence synthesis. †TPT regimens and their costs are shown in appendix 2 (pp 3–4).

Table 1: **Parameter definitions, values, and sources**

	DALYs averted per 1000 people	Tuberculosis cases averted per 1000 people	Tuberculosis deaths averted per 1000 people	Incremental costs per 1000 people*
IGRA and 1HP	149 (55–292)	34 (16–62)	4·5 (1·5–9·4)	44 402 (15 597 to 69 099)
IGRA and 3HP	145 (55–281)	33 (15–61)	4·3 (1·5–9·0)	35 120 (9386 to 56 281)
IGRA and 4R	143 (56–278)	33 (15–59)	4·3 (1·5–8·9)	35 591 (10 551 to 55 331)
IGRA and 9H	132 (51–255)	30 (14–56)	3·9 (1·3–8·1)	39 570 (17 145 to 59 926)
TST and 1HP	142 (54–276)	33 (15–59)	4·3 (1·4–8·8)	19 046 (–6742 to 43 981)
TST and 3HP	138 (53–267)	31 (14–56)	4·1 (1·4–8·5)	8790 (–14 213 to 28 079)
TST and 4R	137 (54–269)	31 (15–56)	4·1 (1·4–8·5)	9257 (–13 725 to 28 557)
TST and 9H	126 (49–246)	28 (13–52)	3·7 (1·3–7·7)	13 230 (–9241 to 32 289)

1HP=1 month of isoniazid and rifapentine every day. 3HP=3 months of isoniazid and rifapentine every week. 4R=4 months of rifampicin every day. 9H=9 months of isoniazid every day. DALYs=disability-adjusted life-years. IGRA=interferon gamma release assays. TST=tuberculin skin test. *Negative incremental costs can arise where cost savings from averted future tuberculosis treatment costs are greater than intervention costs.

Table 2: **Incremental lifetime health benefits and costs for each intervention scenario, as compared to the base-case scenario**

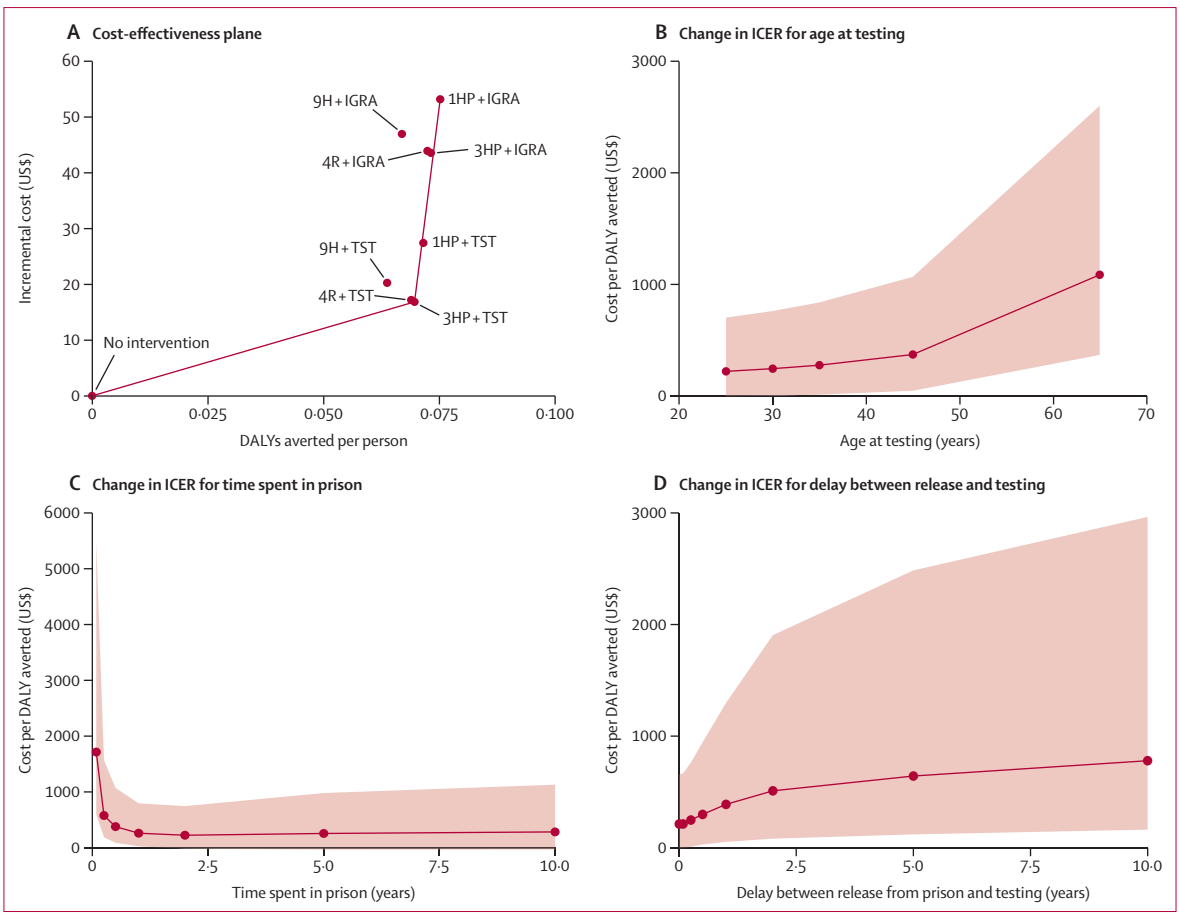

Figure 2: **Cost-effectiveness plane of interventions and base-case scenarios (A) and change in ICER for TST and 3HP versus base case produced by changes in age at testing (B), duration of incarceration (C), and delay between prison release and testing (D)**
Shaded area represents 95% uncertainty interval. The uncertainty of the ICER values are reported in table 2, and not included in panel A for clarity. 1HP=1 month of isoniazid and rifapentine every day. 3HP=3 months of isoniazid and rifapentine every week. 4R=4 months of rifampicin every day. 9H=9 months of isoniazid every day. DALY=disability-adjusted life-year. ICER=incremental cost-effectiveness ratio. IGRA=interferon-gamma release assays. TST=tuberculin skin test.

For our cost-effectiveness analysis (figure 2A), intervention strategies including 9H or 4R and IGRA and 3HP were dominated by TST and 1HP, TST and 3HP, and IGRA and 1HP strategies. Compared with the base-case scenario, TST and 3HP had an ICER of $242 per DALY averted. TST and 1HP was both more effective and costly, with an ICER of $5569 per DALY averted compared with TST and 3HP. When TST and 1HP was compared to the base-case scenario (eg, if the 3HP regimen was not available) the ICER was $383 per DALY averted. The ICER between IGRA and 1HP and TST and 1HP was valued at $7066. Comparing these results to the cost-effectiveness threshold ($6300–9700 per DALY averted) showed that all strategies would be cost-effective compared to the base case. For the optimal test–regimen combination, the choice between TST and 1HP and IGRA and 1HP was inconclusive, with TST and 1HP preferred with a lower cost-effectiveness threshold (ie, when the opportunity cost of spending is higher), and IGRA and 1HP preferred with a higher threshold (appendix 2 pp 4–5).

The incidence of tuberculosis 5 years after prison release was estimated to be 225 (153–485) per 100 000 under the base case and 184 (97–308) per 100 000 with TST and 3HP (appendix 2 p 6).

We did additional analyses to understand how age at screening, duration of incarceration, and delay between release and testing affected intervention outcomes. For these analyses, we used TST and 3HP as the intervention strategy. When we varied age at screening we found that health benefits (DALYs averted) were greatest and the ICER lowest for younger individuals. ICERs ranged from $216 per DALY averted for individuals aged 25 years at screening and up to $1081 per DALY averted for individuals aged 65 years. When we varied the duration of incarceration, we found that health benefits were greatest and ICERs lowest for cohorts with a longer duration of incarceration, although this trend plateaued for durations greater than 2 years. ICERs ranged from $243 per DALY averted for a 2-year duration of incarceration up to $1716 per DALY averted for a 1-month

duration of incarceration. Lastly, we varied the delay between prison release and the intervention being offered. Health benefits were greatest and ICERs lowest with testing soon after release, with both immediate screening and a 1-month delay having ICERs around $208 per DALY averted. ICERs increased with longer delays, with an ICER of $776 per DALY averted estimated for a cohort tested 10 years after prison release (appendix 2 p 5).

For a cost-effectiveness threshold lower than $300 per DALY averted, the base-case scenario of no screening and treatment had the highest probability of being cost-effective (figure 3A). For a threshold between $300 and $7100 per DALY averted, TST and 3HP had the highest probability of being cost-effective and for a threshold higher than $7100 per DALY averted, IGRA and 1HP had the highest probability of being cost-effective. There was substantial uncertainty about the best test regimen.

In one-way deterministic sensitivity analyses the parameters with the greatest influence on the ICER for TST and 3HP versus the base case were the rate of progression to tuberculosis from the latent slow compartment, tuberculosis-specific mortality, the monthly cost of the TPT regimen, the unit cost of tuberculosis diagnosis, the efficacy of the TPT regimen, and the cost of TST (figure 3B), although none changed the conclusion of our analyses. We also tested how elevated reinfection rates after the intervention would affect the cost-effectiveness results. In this analysis, elevated reinfection rates led to higher ICERs, but even with a reinfection rate 50 times higher than the general population, the ICER for TST and 3HP versus the base case was $303 per DALY averted, still well below the cost-effectiveness threshold.

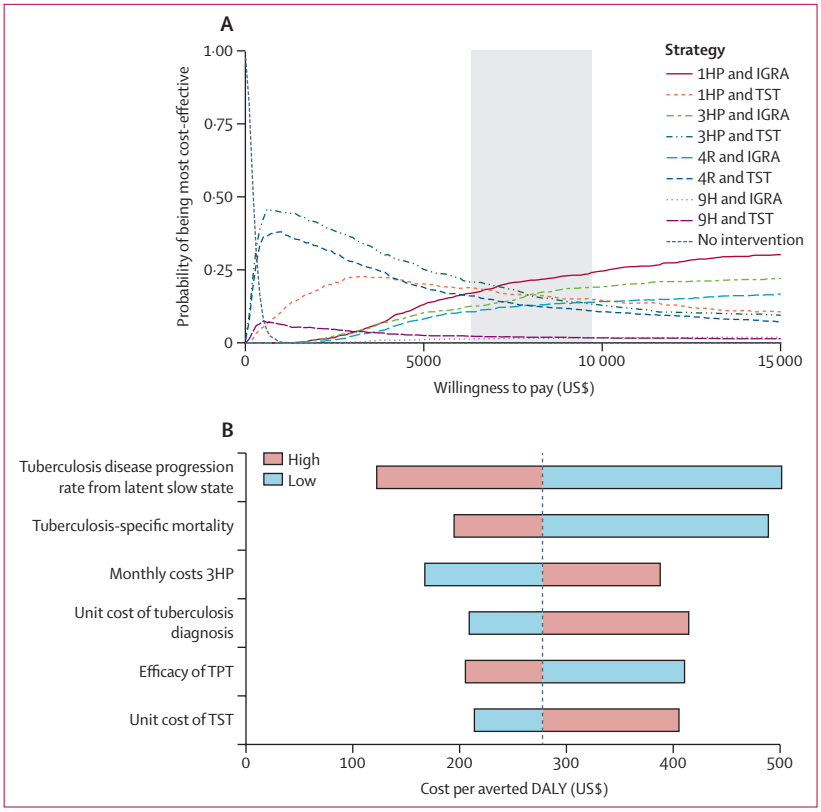

Figure 3: **Cost-effectiveness acceptability curve for base case and intervention scenarios (A) and Tornado diagram showing the six most influential parameters as calculated in the one-way deterministic sensitivity analysis (B)**

Grey-shaded area represents cost-effectiveness threshold in Brazil of 71–109% of the gross domestic product per capita in 2022. 1HP=1 month of isoniazid and rifapentine every day. 3HP=3 months of isoniazid and rifapentine every week. 4R=4 months of rifampicin every day. 9H=9 months of isoniazid every day. DALY=disability-adjusted life-year. IGRA=interferon gamma release assays. TPT=tuberculosis preventive treatment. TST=tuberculin skin test.

Discussion

In this study, we examined the potential health impact and cost-effectiveness of *M tuberculosis* infection screening and TPT for individuals who were formerly incarcerated in Brazil. We found that the intervention would be highly cost-effective in this setting, with a cost per DALY averted estimated to be less than a tenth of the cost-effectiveness threshold adopted for this analysis. This result was robust to uncertainty in input parameters and was true for all subgroups examined. Across all scenarios, all combinations of test and regimen were highly cost-effective compared with the base-case scenario, implying that any choice of test and regimen would be beneficial. The analysis was inconclusive as to which strategy should be preferred at the suggested cost-effectiveness threshold. Among the test and regimen options examined, we found that scenarios using IGRA for *M tuberculosis* infection testing produced greater health benefits than those using TST, which is consistent with published research.[51] The analysis also found that shorter TPT regimens were more effective than longer regimens. Shorter regimens can have lower default rates, and were, in this study, assumed to have similar efficacy. Therefore, shorter regimens had greater health effects and more favourable cost-effective estimates.[52,53]

We also analysed how age at testing, duration of incarceration, and time between release and testing affected study results. We found that the health impact of the intervention was greater for younger individuals, with a greater life expectancy over which tuberculosis could develop, and a greater number of life-years lost when tuberculosis death occurs at a younger age.

Health benefits were also estimated to be greater for individuals with a longer duration of incarceration, with these individuals more likely to acquire infection before release, and therefore having more to gain from the preventive intervention. This effect plateaued for durations of incarceration greater than 2 years.

Finally, we found that health benefits were greatest for individuals tested soon after prison release. As the risk of developing tuberculosis declines with increasing time since infection, individuals tested shortly after release are more likely to have recent infection and experience high

risk of tuberculosis in the absence of TPT. For each of these subgroup analyses, greater health benefits were associated with lower (ie, more favourable) cost-effectiveness ratios.

This study has several limitations. First, we did not explicitly simulate reincarceration among the target population. An average of 21% of individuals who were formerly incarcerated return to prison within the first year of release, increasing to 38.9% after 5 years since release.[54] Reincarceration could lead to reinfection among individuals who had received TPT, reducing intervention benefits. We tested how study results would be affected by higher reinfection rates, and found that cost-effectiveness conclusions were robust to reinfection rates up to 50 times higher than those assumed in the main analysis. Reincarceration could also reduce the fraction of individuals completing the TPT regimen. Although higher rates of discontinuation were associated with lower health benefits, the intervention was found to be cost-effective across the range of discontinuation rates examined in this study. Second, there was substantial uncertainty around several parameters in the analysis, especially considering the scarce literature on the study population. Because this uncertainty is included in the cost-effectiveness analysis, the overall intervention effects were estimated imprecisely with wide uncertainty intervals. Further empirical research on tuberculosis burden and intervention options for current and formerly incarcerated populations could enable more precise estimates. It is important to note that the major cost-effectiveness conclusion—that some form of TPT would be cost-effective for formerly incarcerated individuals—is robust to these uncertainties, and the wide intervals are not a reason to delay decision making.[55] Under a pessimistic scenario in which the ICER is at the upper limit of the confidence interval, the intervention would still be cost-effective. Third, it is possible that individuals accepting the intervention would differ systematically from the overall population of individuals who were formerly incarcerated. We did not investigate these selection effects. It is possible that these selection effects could promote cost-effectiveness (for example, if individuals choosing to be screened are more likely to accept and complete TPT), but they could also have the opposite effect (if individuals choosing to be screened are systematically healthier or with lower infectious exposure in prison). This finding represents an additional unmodelled source of uncertainty in the study results. Fourth, we did not account for tuberculosis drug resistance in the analysis, which could potentially reduce intervention effectiveness if rates of drug-resistant tuberculosis were high. Lastly, this analysis estimates national average results. Intervention impact and cost-effectiveness will probably vary across regions and prisons, related to variations in the risks of *M tuberculosis* exposure and other factors.

Although our study found the intervention to be highly cost-effective, it is possible that uptake would be lower than assumed among the target population, given that *M tuberculosis* infection does not produce symptoms that might motivate an individual to seek screening, and the benefits of avoiding future disease risks might not have great saliency for these individuals. Individuals might avoid any linkage to incarceration because of social stigma, affecting the acceptance of treatment. Given the highly favourable cost-effectiveness ratios, additional resources could be devoted to improving acceptance and completion rates without compromising intervention cost-effectiveness. We did not account for reductions in tuberculosis transmission resulting from the intervention, which could further benefit both prison populations and surrounding communities. Because of high recidivism rates, reduction in tuberculosis transmission among individuals who were formerly incarcerated might also affect tuberculosis transmission risks in prisons. Individuals who were formerly incarcerated are often from a lower socioeconomic status, and the introduction of the intervention could potentially contribute to reducing disparities.[56]

In summary, tuberculosis prevention among individuals who were formerly incarcerated has received little attention, but this population is large and has a high burden of tuberculosis disease. The findings of this study suggest that screening and treatment of *M tuberculosis* infection would be a cost-effective and effective intervention for this population.

Contributors

AvLT, DMP, KA, MS, PB, MCC, TC, and NAM conceptualised the research. AvLT, FK, JRA, TC, and NAM developed the methodology used, and FK, DMP, JNdBS, LCA, MS, PB, FDCJ, JC, JRA, MCC, and TC validated the project. The research was supervised by CV and NAM, and coordinated by NAM. AvLT curated data, performed the formal analysis, did the investigation, administered the project, and did the visualisation. NAM did the funding acquisition, and resources were provided by JNBS, KA, LCA, and PB. The original draft was written by AvLT and NAM, and reviewed, edited, and approved by all authors. AvLT and NAM have full access to all data in the study. All authors read and approved the final version of the article.

Declaration of interests

We declare no competing interests.

Data sharing

All data and analytic code related to the analysis are available at https://zenodo.org/records/11065395?token=eyJhbGciOiJIUzUxMiJ9.eyJpZCI6IjA2ZTExMGM1LWQxZTQtNDczYi1iYThhLWE1MmUyNGRlYTRiZSIsImRhdGEiOnt9LCJyYW5kb20iOiJlMjk1NjM0OWZmNjZjODI3YzBiZjdkMjdmOWRiMDBkMCJ9.lEc6qaOp6NL4eAy-4O98Jz9KI_d6Dhov-aYHRRMHntkFZFPfssXoqulFMTsl6ZcQRZjmg0pb-2KXSyLSywiU9A.

References

1 Mabud TS, de Lourdes Delgado Alves M, Ko AI, et al. Evaluating strategies for control of tuberculosis in prisons and prevention of spillover into communities: an observational and modeling study from Brazil. *PLoS Med* 2019; **16:** e1002737.

2 Carbone AdSS, Paião DSG, Sgarbi RVE, et al. Active and latent tuberculosis in Brazilian correctional facilities: a cross-sectional study. *BMC Infect Dis* 2015; **15:** 24.

3 Baussano I, Williams BG, Nunn P, Beggiato M, Fedeli U, Scano F. Tuberculosis incidence in prisons: a systematic review. *PLoS Med* 2010; **7:** e1000381.

4 Vynnycky E, Fine P. The natural history of tuberculosis: the implications of age-dependent risks of disease and the role of reinfection. *Epidemiol Infect* 1997; **119:** 183–201.

5 WHO. Tuberculosis: key facts 2023. https://www.who.int/news-room/fact-sheets/detail/tuberculosis#:~:text=Worldwide%2C%20TB%20is%20the%2013th,all%20countries%20and%20age%20groups (accessed Dec 9, 2023).

6 WHO. Tuberculosis in prisons 2023. https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2023/featured-topics/tb-in-prisons (accessed Dec 9, 2023).

7 Li Y, de Macedo Couto R, Pelissari DM, et al. Excess tuberculosis cases and deaths following an economic recession in Brazil: an analysis of nationally representative disease registry data. *Lancet Glob Health* 2022; **10:** 1463–72.

8 Ministerio da Saude. Sistema de Informação de Agravos de Notificação. 2022. https://datasus.saude.gov.br/transferencia-de-arquivos/ (accessed Nov 5, 2023).

9 Martinez L, Warren JL, Harries AD, et al. Global, regional, and national estimates of tuberculosis incidence and case detection among incarcerated individuals from 2000 to 2019: a systematic analysis. *Lancet Public Health* 2023; **8:** 511–19.

10 Sacchi FPC, Praça RM, Tatara MB, et al. Prisons as reservoir for community transmission of tuberculosis, Brazil. *Emerg Infect Dis* 2015; **21:** 452–55.

11 Dale KD, Karmakar M, Snow KJ, Menzies D, Trauer JM, Denholm JT. Quantifying the rates of late reactivation tuberculosis: a systematic review. *Lancet Infect Dis* 2021; **21:** 303–17.

12 WHO. The End TB strategy. Geneva: World Health Organization, 2015.

13 Bagcchi S. Brazil tackles its tuberculosis burden. *Newsdesk* 2023; **23:** 790.

14 Narayan A, Salindri AD, Keshavjee S, et al. Prioritizing persons deprived of liberty in global guidelines for tuberculosis preventive treatment. *PLoS Med* 2023; **20:** e1004288.

15 Paião DSG, Lemos EF, Carbone AdSS, et al. Impact of mass-screening on tuberculosis incidence in a prospective cohort of Brazilian prisoners. *BMC Infect Dis* 2016; **16:** 533.

16 Pivetta de Araujo RC, Martinez L, da Silva Santos A, et al. Serial mass screening for tuberculosis among incarcerated persons in Brazil. *Clin Infect Dis* 2024; **78:** 1669–76.

17 Uwe Siebert OA, Bayoumi AM, Jahn B, et al. State-transition modeling: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force 3. *J Int Soc Pharmacoecon Outcome Res* 2012; **15:** 812–20.

18 Ministério da Saúde. Manual de recomendações para o controle da tuberculose no Brasil. In: Transmissíveis DdVdD. Brazil: Ministério da Saúde, 2019.

19 Sutherland I. The ten-year incidence of clinical tuberculosis following "conversion" in 2550 individuals aged 14 to 19 years: TSRU progress report. The Hague: KNCV, 1968.

20 Farebee S. Controlled chemoprophylaxis trials in tuberculosis: a general review. *Adv Tuberculosis Res* 1970; **17:** 28–106.

21 Andrews JR, Noubary F, Walensky RP, Cerda R, Losina E, Horsburgh CR. Risk of progression to active tuberculosis following reinfection with *Mycobacterium tuberculosis*. *Clin Infect Dis* 2012; **54:** 784–91.

22 Menzies NA, Wolf E, Connors D, et al. Progression from latent infection to active disease in dynamic tuberculosis transmission models: a systematic review of the validity of modelling assumptions. *Lancet Infect Dis* 2018; **18:** 228–38.

23 Tiemersma EW, van der Werf MJ, Borgdorff MW, Williams BG, Nagelkerke NJD. Natural history of tuberculosis: duration and fatality of untreated pulmonary tuberculosis in HIV negative patients: a systematic review. *PLoS One* 2011; **6:** e17601.

24 UN Population Division. Life table Brazil. New York: United Nations, 2019.

25 WHO. WHO consolidated guidelines on tuberculosis. Module 3: diagnosis. Tests for tuberculosis infection. Geneva: World Health Organization, 2022.

26 WHO. Guidelines on the management of latent tuberculosis infection. Geneva: World Health Organization, 2018.

27 Ministério da Saúde. Protocolo de vigilância da infecção latente pelo *Mycobacterium tuberculosis* no Brasil. In: Transmissíveis DdDdCCeIS, 2nd edn. Brasília: Ministério de Saúde, 2022.

28 Ades AE, Sculpher M, Sutton A, et al. Bayesian methods for evidence synthesis in cost-effectiveness analysis. *Pharmacoecon* 2006; **24:** 1–19.

29 McQuaid C, Clarkson M, Bellerose M, Floyd K, White R. An approach for improving the quality of country-level TB modelling. *Int J Tuberculosis Lung Dis* 2021; **25:** 614–19.

30 Steffen RE, Pinto M, Kritski A, Trajman A. Cost-effectiveness of newer technologies for the diagnosis of *Mycobacterium tuberculosis* infection in Brazilian people living with HIV. *Sci Rep* 2020; **10:** 21823.

31 Doan TN, Eisen DP, Rose MT, Slack A, Stearnes G, McBryde ES. Interferon-gamma release assay for the diagnosis of latent tuberculosis infection: a latent-class analysis. *PLoS One* 2017; **12:** 11.

32 Zhang Y, Zhou G, Shi W, et al. Comparing the diagnostic performance of QuantiFERON-TB Gold Plus with QFT-GIT, T-SPOT.TB and TST: a systematic review and meta-analysis. *BMC Infect Dis* 2023; **23:** 40.

33 WHO. WHO consolidated guidelines on tuberculosis. Module 2: systematic screening for tuberculosis disease. Geneva: World Health Organization, 2021.

34 Zenner D, Beer N, Harris RJ, Lipman MC, Stagg HR, van der Werf MJ. Treatment of latent tuberculosis infection: an updated network meta-analysis. *Ann Int Med* 2017; **167:** 248–55.

35 International Union Against Tuberculosis Committee on Prophylaxis. Efficacy of various durations of isoniazid preventive therapy for tuberculosis: five years of follow-up in the IUAT trial. *Bull World Health Organ* 1982; **60:** 555–64.

36 Sterling TR, Njie G, Zenner D, et al. Guidelines for the treatment of latent tuberculosis infection: recommendations from the national tuberculosis controllers association and CDC, 2020. *MMWR Recomm Rep* 2020; **69:** 1–11.

37 Swindells S, Ramchandani R, Gupta A, et al. One month of rifapentine plus isoniazid to prevent HIV-related tuberculosis. *New Engl J Med* 2019; **380:** 1001–11.

38 Araújo NCN, Cruz CMS, Arriaga MB, et al. Determinants of losses in the latent tuberculosis cascade of care in Brazil: a retrospective cohort study. *Int J Infect Dis* 2020; **121:** 1.

39 Nsengiyumva NP, Campbell JR, Oxlade O, et al. Scaling up target regimens for tuberculosis preventive treatment in Brazil and South Africa: an analysis of costs and cost-effectiveness. *PLoS Med* 2022; **19:** e1004032.

40 Bastos ML, Oxlade O, Campbell JR, Faerstein E, Menzies D, Trajman A. Scaling up investigation and treatment of household contacts of tuberculosis patients in Brazil: a cost-effectiveness and budget impact analysis. *Lancet Region Health Americas* 2022; **8:** 100166.

41 Ministério da Saúde Secretaria Executiva. Sistema Integrado de Administração de Material. Brasília: Ministério da Saúde Secretaria Executiva, 2021.

42 Loureiro RB, Maciel ELN, Caetano R, et al. Cost-effectiveness of QuantiFERON-TB Gold in-tube versus tuberculin skin test for diagnosis and treatment of latent tuberculosis infection in primary health care workers in Brazil. *PLoS One* 2019; **14:** e0225197.

43 Steffen RE, Caetano R, Pinto M, et al. Cost-effectiveness of Quantiferon-TB Gold-in-tube versus tuberculin skin testing for contact screening and treatment of latent tuberculosis infection in Brazil. *PLoS One* 2013; **8:** e59546.

44 Santos AdS, de Oliveira RD, Lemos EF, et al. Yield, efficiency, and costs of mass screening algorithms for tuberculosis in Brazilian prisons. *Clin Infect Dis* 2020; **72:** 771–77.

45 Salomon JA, Haagsma JA, Davis A, et al. Disability weights for the Global Burden of Disease 2013 study. *Lancet Glob Health* 2015; **3:** e713–23.

46 Wilkinson T, Sculpher MJ, Claxton K, et al. The international decision support initiative reference case for economic evaluation: an aid to thought. *J Int Soc Pharmacoecon Outcome Res* 2016; **19:** 921–27.

47 Ochalek J, Lomas J, Claxton K. Estimating health opportunity costs in low-income and middle-income countries: a novel approach and evidence from cross-country data. *BMJ Glob Health* 2018; **3:** e000964.

48 World Bank. Global domestic product per capita (current US$). 2022. https://data.worldbank.org/country/BR (accessed Sept 15, 2023).

49 Briggs A, Weinstein MC, Fenwick EAL, et al. Model parameter estimation and uncertainty: a report of the ISPOR-SMDM modeling good research practices task force-6. *Value Health* 2012; **15:** 835–42.

50 Fenwick E, Marshall DA, Levy AR, Nichol G. Using and interpresting cost-effectiveness acceptability curves: an example using data from a trial of management strategies for atrial fibrillation. *BMC Health Serv Res* 2006; **6:** 52.

51 Kowada A. Cost-effectiveness of interferon gamma release assay for entry tuberculosis screening in prison. *Epidemiol Infect* 2013; **141:** 2224–34.

52 Doan TN, Fox GJ, Meehan MT, et al. Cost-effectiveness of 3 months of weekly rifapentine and isoniazid compared with other standard treatment regimens for latent tuberculosis infection: a decision analysis study. *J Antimicrob Chemo* 2018; **74:** 218–27.

53 Holland DP, Sanders GD, Hamilton CD, Stout JE. Costs and cost-effectiveness of four treatment regimens for latent tuberculosis infection. *Am J Respir Crit Care Med* 2009; **179:** 1055–60.

54 Carrillo B, Sampaio B, Britto DGC, et al. Reincidência Criminal no Brasil. 2022. https://www.gov.br/senappen/pt-br/assuntos/noticias/depen-divulga-relatorio-previo-de-estudo-inedito-sobre-reincidencia-criminal-no-brasil/reincidencia-criminal-no-brasil-2022.pdf/view (accessed Dec 14, 2023).

55 Claxton K. The irrelevance of inference: a decision-making approach to the stochastic evaluation of health care technologies. *J Health Econ* 1999; **18:** 341–64.

56 Pelissari DM, Diaz-Quijano FA. Impact of incarceration on tuberculosis incidence and its interaction with income distribution inequality in Brazil. *Transact Royal Soc Trop Med Hygiene* 2019; **114:** 23–30.