

Yield, Efficiency, and Costs of Mass Screening Algorithms for Tuberculosis in Brazilian Prisons

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(See the Editorial Commentary by Woodman and Grandjean on pages 778–9.)

Background. Tuberculosis (TB) is a major cause of morbidity and mortality among incarcerated populations globally. We performed mass TB screening in 3 prisons and assessed yield, efficiency, and costs associated with various screening algorithms.

Methods. Between 2017 and 2018, inmates from 3 prisons in Brazil were screened for TB by symptom assessment, chest radiography, sputum testing by Xpert MTB/RIF fourth-generation assay, and culture. Chest radiographs were scored by an automated interpretation algorithm (Computer-Aided Detection for Tuberculosis [CAD4TB]) that was locally calibrated to establish a positivity threshold. Four diagnostic algorithms were evaluated. We assessed the yield (percentage of total cases found) and efficiency (prevalence among those screened) for each algorithm. We performed unit costing to estimate the costs of each screening or diagnostic test and calculated the cost per case detected for each algorithm.

Results. We screened 5387 prisoners, of whom 214 (3.9%) were diagnosed with TB. Compared to other screening strategies initiated with chest radiography or symptoms, the trial of all participants with a single Xpert MTB/RIF sputum test detected 74% of all TB cases at a cost of US\$249 per case diagnosed. Performing Xpert MTB/RIF screening tests only on those with symptoms had a similar cost per case diagnosed (US\$255) but missed 35% more cases (73 vs 54) as screening all inmates.

Conclusions. In this prospective study in 3 prisons in a high TB burden country, we found that testing all inmates with sputum Xpert MTB/RIF was a sensitive approach, while remaining cost-efficient. These results support use of Xpert MTB/RIF for mass screening in TB-endemic prisons.

Keywords. mass screening; tuberculosis; algorithms; prisons; cost-effectiveness.

Tuberculosis (TB) is the leading cause of death by an infectious disease worldwide [1] and as a response, the World Health Assembly set a goal to reduce the global TB incidence by 90% by 2035 [2]. Despite an elevated focus on TB and increased funding, the TB burden is declining by only 1%–2% per year globally. To reach global targets, complementary interventions are needed to supplement current TB control. Recently, there has been a push to target interventions to populations with a high TB burden to reduce disease incidence and transmission to the broader community [3, 4].

Prisons frequently have a very high burden of TB [5]. A meta-analysis of 19 studies found that the incidence of TB in prisons was 23 times greater than the surrounding population [5]. This high incidence leads to markedly elevated transmission rates.

For example, 3 prisoner cohorts from Brazil, Colombia, and Iran have shown annual tuberculin conversion rates between 15% and 25% [6–8]. Effective case detection for TB in prisons is necessary to reduce ongoing transmission.

Despite the high rates of TB in prisoners and the potential importance of this population in the overall epidemic [3, 5, 9], few studies have assessed the efficiency and costs of different approaches for screening for TB among incarcerated populations [7]. Studies reporting the yield of TB detected in prisons rarely compare distinct screening modalities or report their costs. Additionally, the use of sensitive molecular diagnostic tests, such as the Xpert MTB/RIF assay, for TB screening among prisoners has not been widely explored. Studies using mathematical modeling suggest that annual mass screening can reduce the incidence of TB in prisons [3, 10]. However, there are no specific guidelines on how screening should be performed. Due to costs and a lack of evidence on effective screening approaches in this population, few prisons in low- and middle-income countries perform systematic screening for TB. Our objective was to identify effective and efficient approaches to TB screening in prisons that could be implemented in low- and middle-income countries.

Received 24 September 2019; editorial decision 3 January 2020; accepted 13 February 2020; published online February 17, 2020.

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Clinical Infectious Diseases® 2021;72(5):771–7

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METHODS

Study Population

This study was carried out in 3 prisons in Mato Grosso do Sul, Brazil. Brazil's national prison population is > 700 000 individuals, the third largest globally [11]. Three prisons were included in this study: Penitenciária Estadual de Dourados (PED), Estabelecimento Penal Jair Ferreira de Carvalho (EPJFC), and Instituto Penal de Campo Grande (IPCG). These prisons exclusively incarcerate males ≥ 18 years old and were selected because they are the largest in the state and had the highest TB infection and disease rates in preliminary studies [7, 12].

Study Procedures

All prisoners were invited to participate, and those who accepted provided written informed consent. The study was approved by the Federal University of Grande Dourados, the National Committee on Research Ethics (number 2.195.047), and the Institutional Review Board of Stanford University (number 40285). Each participant was then interviewed using a standardized questionnaire to collect demographic and clinical information. We asked each participant about TB-related symptoms according to World Health Organization (WHO) guidelines [13, 14]. All participants were instructed to produce a sputum sample with a target volume of at least 2 mL. On this primary sample, the Xpert MTB/RIF assay (Cepheid, Sunnyvale; fourth generation; hereinafter Xpert) was performed; the remainder of the sample was transported to the support laboratory for culture. A second sputum sample was collected on the following day for a second culture. Participants who were unable to produce sputum were coached by nursing staff; however, sputum induction was not performed, and many participants were unable to produce a sample. Participants without sufficient samples were included in the study.

All participants underwent posterior-anterior chest radiography (CXR). Chest radiographs were then evaluated with Computer-Aided Detection for Tuberculosis (CAD4TB) software version 5 [15]. CAD4TB assigns a quality assessment to a CXR, produces a heat map indicating areas with possible abnormalities, and designates a score between 1 and 100 related to the likelihood of radiological abnormalities suggestive of a TB diagnosis. CAD4TB was calibrated with training data from radiographic images of participants with ($n = 80$) and without ($n = 200$) microbiologically confirmed TB. Training data demonstrated high accuracy (area under the curve = 0.88), with a sensitivity and specificity > 80% using a CAD4TB score ≥ 60 . Participants with a CAD4TB score ≥ 60 were clinically reevaluated; those who had been unable to produce sputum on the first occasion were given another opportunity and additional coaching to produce a sample for testing by Xpert assay. Those participants with negative results or who were still unable to produce sputum were assessed by a physician. All TB cases identified during screening were provided free treatment according to national guidelines [16].

Derivation of Mass Diagnostic Screening Algorithms

All participants were prospectively and systematically screened as outlined above; we then retrospectively evaluated 4 hypothetical, intensive screening algorithms (Figure 1) consisting of more limited sets of diagnostics:

- Strategy 1: Sputum testing by Xpert for all participants who could produce sputum at the moment of questionnaire, regardless of presence of symptoms.
- Strategy 2: Sputum testing by Xpert only for those who reported any TB-related symptom of any duration and who could produce sputum at the moment of questionnaire.
- Strategy 3: CXR with CAD4TB scoring for all participants. Those with CAD4TB score ≥ 60 underwent sputum testing by Xpert.
- Strategy 4: Symptom screening, followed by sputum Xpert testing for participants who reported a TB-related symptom. Those without any TB symptoms underwent CXR with CAD4TB scoring. Sputum collection and Xpert testing were then offered to participants with a CAD4TB score ≥ 60 .

Outcome Definitions

We followed national Brazilian guidelines and WHO definitions for TB diagnosis. We defined a TB case as any individual with a positive sputum Xpert, sputum culture, or with a physician diagnosis based on clinical-epidemiological data and radiographic abnormalities. All participants with TB were administered a rapid human immunodeficiency virus (HIV) test and evaluated through a nursing and medical examination.

Analytical Approach and Cost Evaluation

We calculated the cost of each screening procedure: symptom screening interviews, Xpert, culture, and radiographic and clinical evaluations. These costs include equipment, maintenance, consumables, and personnel time. The [Supplementary Table S1](#) has description of the full cost for each diagnostic procedure ([Supplementary Appendix](#)).

In our calculations, we assumed the equipment used during mass screening would remain useful for a period of 10 years and amortized the cost over this period. Personnel time was calculated based on the salary of staff members involved in each screening component, time devoted to each component of screening, and the number of individuals who could be screened during that unit time. We calculated average unit cost by dividing total cost of each diagnostic procedure by the total number of procedures during the study period. The cost of each Xpert cartridge was US\$9.90.

To calculate the cost per case detected, we assumed the definition of fixed and variable costs. Fixed costs are costs that apply to the entire cohort, regardless of how many people are screened, such as purchasing and maintaining equipment and software. Variable costs are costs related to use, such as human

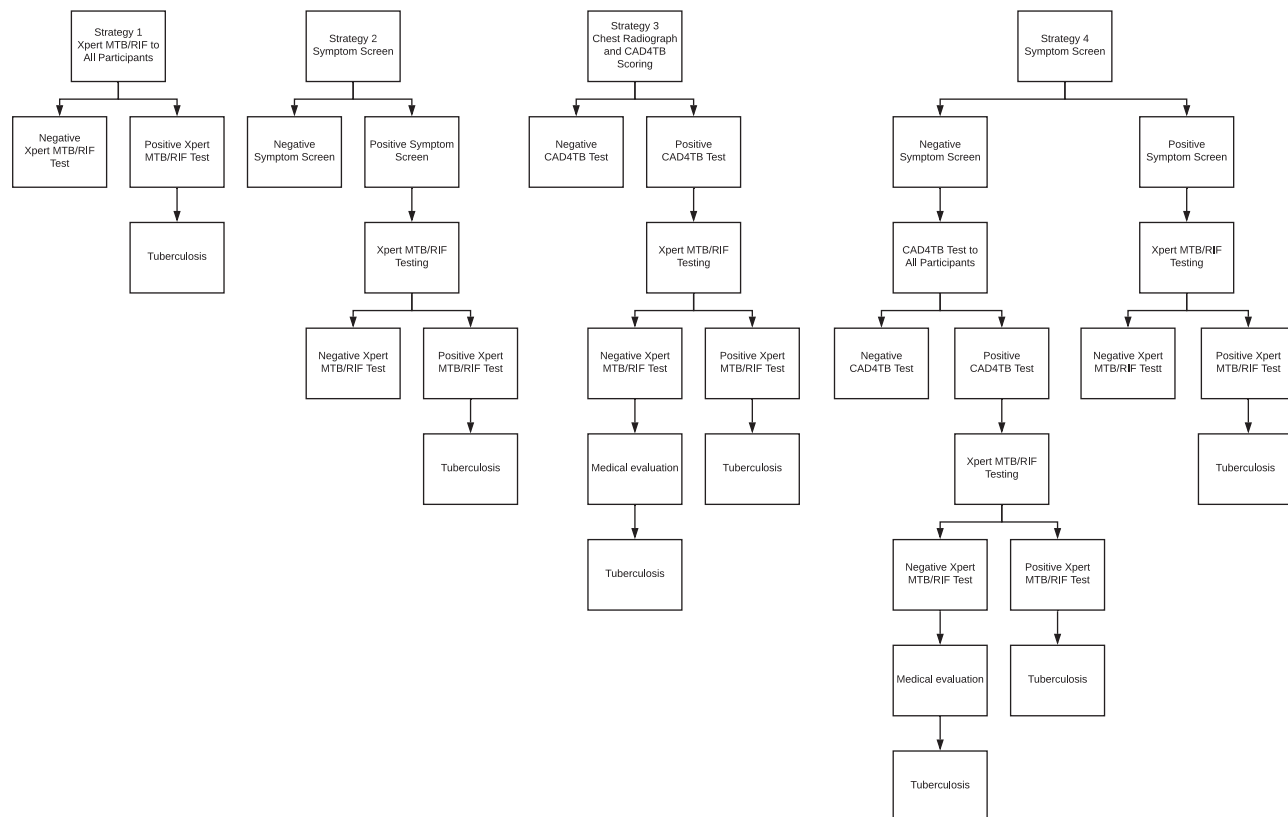


Figure 1. Outline of tuberculosis screening strategies assessed among prisoners in the study. Abbreviations: CAD4TB, Computer-Aided Detection for Tuberculosis; MTB, *Mycobacterium tuberculosis*; RIF, rifampicin.

resources, inputs, and evaluation of each radiographic image in CAD4TB. The cost per case detected was calculated for each strategy by multiplying the average unit cost by the number of procedures performed in each strategy and then dividing by the cases detected in the strategy. The values in Brazilian reais were converted to US dollars using the quotation of 28 November 2018 (R\$3.87 = US\$1.00).

RESULTS

Study Population

Between November 2017 and July 2018, we screened 5387 of 6054 eligible study participants (88.9%). These three prisons can hold up to 1610 prisoners, but currently hold 6054 incarcerated individuals in total and have high turnover rates (Supplementary Appendix). Reasons for not participating included lack of interest, lack of clothing to leave the cell, and fear of meeting members of rival groups. Participating inmates had a median age of 30.5 years (Table 1). More than half of participants were smokers (58.3%) and used some type of illicit drug in the past year (58.8%), and 70.3% were previously incarcerated. More than 71.4% of participants reported knowing a person diagnosed with TB, and 8.2% reported having prior TB. During the study period, a total of 214 participants were diagnosed with pulmonary TB, equating to a

prevalence of 3973 per 100 000 participants (95% confidence interval, 3483–4528). Disaggregating by prison, we identified TB prevalence of 5567/100 000 (101/1814) in EPJFC, 3607/100 000 (82/2273) in PED, and 2384/100 000 (31/1300) in IPCG.

Of the diagnosed cases on the initial visit, 172 (80.3%) were diagnosed by the Xpert assay and sputum culture. At the initial visit, sputum was obtained from 1467 inmates. Among these, Xpert was performed on almost all participants (1452 [98.9%]) and detected 160 TB cases (Figure 2). Culture was performed on 1385 participants and 12 additional cases were identified by culture. Sputum smear tests were performed on 1386 participants; among the 214 TB cases who had smear microscopy performed, 49 (22.8%) had a positive smear. All TB cases that tested smear-positive were positive by Xpert. Among 1295 participants who were culture and/or Xpert negative, 261 had a CAD4TB score ≥ 60 . According to the study protocol, these participants were reevaluated for TB, 114 did Xpert, and 22 were diagnosed (11 by Xpert and 11 by clinical evaluation). Among participants who did not produce a sputum sample at the initial visit ($n = 3920$), 523 (13.3%) had a CAD4TB score ≥ 60 . A second attempt was made to collect sputum among these participants, of which 155 (29.6%) were successful and 9 were Xpert positive. A further

Table 1. Sociodemographic Characteristics and Risk Factors for Tuberculosis Among Screened Inmates

Variables	Total (N = 5387)	TB Cases (n = 214)	No TB (n = 5173)	P Value
Prison unit				
PED	2272 (42.2)	82 (38.3)	2191 (42.4)	.24
EPJFC	1814 (33.7)	101 (47.2)	1713 (33.1)	<.01
IPCG	1300 (24.1)	31 (14.5)	1269 (24.5)	<.01
Median age, y (IQR)	30.5 (25–37)	30 (25–37)	31 (25–37)	<.01
Ethnicity				
Mixed	3312 (61.5)	136 (63.6)	3176 (61.3)	.52
White	1306 (24.2)	49 (22.9)	1257 (24.3)	.64
Black	617 (11.5)	23 (10.7)	593 (11.4)	.76
Indigenous	144 (2.6)	6 (2.8)	138 (2.6)	>.99
Asian	8 (0.1)	0 (0.0)	8 (0.2)	>.99
< 8 y of schooling	3540 (65.7)	154 (72.0)	3386 (65.4)	.04
Current smoker	3139 (58.3)	161 (75.2)	2978 (57.5)	<.01
Illicit drug use over the last year	3172 (58.8)	169 (78.9)	3003 (58.0)	<.01
BCG vaccinated	4736 (87.9)	185 (86.4)	4551 (87.9)	.49
Previous TB	482 (8.2)	56 (26.2)	426 (8.2)	<.01
Know someone with TB	3849 (71.4)	181 (84.6)	3668 (70.9)	<.01
Report any WHO TB symptoms	2127 (39.4)	174 (81.3)	1953 (37.7)	<.01
Report cough	1527 (28.3)	151 (70.6)	1376 (26.6)	<.01
Previously incarcerated	3786 (70.3)	167 (78.0)	3619 (70.0)	<.01

Data are presented as no. (%) unless otherwise indicated.

Abbreviations: BCG, Bacillus Calmette-Guérin; EPJFC, Estabelecimento Penal Jair Ferreira de Carvalho; IPCG, Instituto Penal de Campo Grande; IQR, interquartile range; PED, Penitenciária Estadual de Dourados; TB, tuberculosis; WHO, World Health Organization.

11 cases were clinically diagnosed after physician reevaluation. Among cases of active TB, 4 (1.9%) were HIV positive.

Accuracy and Yield of Symptom- and Radiograph-based Screening

In the initial screening interview, 2127/5387 patients (39.5%) reported at least 1 WHO-defined TB symptom; the most common of the symptoms was cough (71.8%). Symptom screening alone had a sensitivity and specificity of 81.3% and 61.6%, respectively. If screening was initiated based on cough alone rather than a comprehensive symptom screen, 151 (70.6%) cases would be detected (Table 2). The sensitivity of CXR with a CAD4TB score ≥ 60 was 77.1% and specificity was 85.6%.

The prevalence of TB was very low (0.2%) among participants with no symptoms and a CAD4TB score < 60 , and this group comprised just over half (51.6%) of all participants. Prevalence among participants with no TB symptoms but CAD4TB score ≥ 60 , comprising 8.7% of the cohort, was 7.0%. Among the 22.0% of participants with cough and CAD4TB score < 60 , prevalence was 3.0%. The highest-risk group consisted of participants with both cough and CAD4TB score ≥ 60 , in whom prevalence was 34.0%; although only 6.3% of participants met both criteria, this accounted for 53.8% of all TB cases detected.

Costs and Efficiency of Screening Strategies

Among diagnostic modalities used during mass screening, the highest cost per participant was for Xpert (US\$19.20), followed by CXR with CAD4TB scoring (US\$6.28), clinical evaluation (US\$2.60), and symptom screening interviews (US\$1.90)

(Table 3). The costliest component of Xpert was consumables (54.8%). For CAD4TB score, CXR, human resources, equipment, and CAD4TB score analysis contributed almost equally to main costs (29.6%, 29.0%, and 29.8%, respectively).

The cost per case detected for all strategies ranged from US\$249 to US\$395 (Table 4). Strategy 1 (Xpert assay for all participants) resulted in the second highest yield, detecting 74% of all cases, at lowest cost (US\$249) per case detected. Strategy 2 (Xpert for individuals with any symptom) had a low cost per case detected (US\$255) but resulted in lower yield (65%) compared with strategies 1 and 4. Strategies 2 and 3 had lower yield (65% and 64%, respectively) than strategies 1 and 4. And strategies 3 and 4 had a higher cost per case diagnosed (US\$370 and US\$395, respectively).

DISCUSSION

Tuberculosis is a major infectious disease problem within prisons worldwide. However, there is a dearth of evidence concerning how to effectively detect TB while controlling costs in these environments. As a result, screening modalities in prisons globally remain variable, with few high-TB-burden countries enacting systematic screening policies in correctional facilities. In 3 prisons in Brazil, we found a very high prevalence (3973 per 100 000) of TB through systematic screening of inmates. This prevalence is higher to the identified in other studies in prisons in Brazil and other countries [17–21].

The strategies 1 and 4 had similar yields. We found that systematic Xpert testing among all individuals able to produce

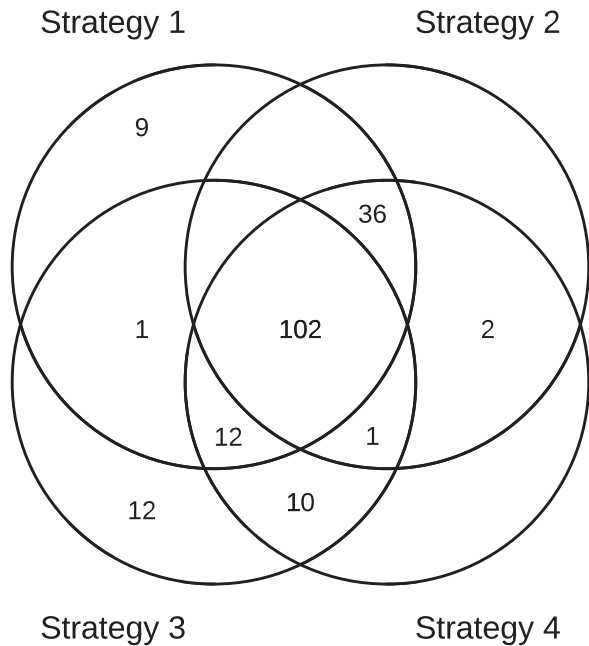


Figure 2. Tuberculosis (TB) cases overlap of screening strategies. Strategy 1: Xpert MTB/RIF assay for all prisoners. Strategy 2: Xpert test only for those who reported any TB symptom. Strategy 3: Chest radiography, those with Computer-Aided Detection for Tuberculosis (CAD4TB) score ≥ 60 undergo Xpert test. Strategy 4: Symptom screening, followed by Xpert test, those without any TB symptoms undergo chest radiography with CAD4TB scoring followed by Xpert test. Abbreviations: MTB, *Mycobacterium tuberculosis*; RIF, rifampicin.

sputum was effective at a modest cost per case diagnosed of US\$249 dollars, and detected only 3 fewer cases compared to strategy 4, which detected the most due to radiographically diagnosed cases. Implementing a symptom screen to identify individuals for sputum testing had a similar efficiency at US\$255 per case detected. Strategies involving CXR were most costly and did not increase the overall yield compared with sputum Xpert testing alone. We also conducted a sensitivity analysis using a US\$5.00 value for Xpert MTB/RIF cartridges. Under this pricing assumption for Xpert cartridges, Strategy 1 remained the most effective and efficient strategy.

We believe this further supports our primary analysis (Supplementary Appendix). Together, these results suggest that testing all inmates able to produce sputum using Xpert may be an effective and affordable strategy in high-burden prisons.

There has been debate over the reliability of symptom screening to triage the use of diagnostics in high-risk populations, due to limitations in both sensitivity and specificity [22, 23]. We found that approximately 39.5% of all inmates reported at least 1 WHO-defined TB symptom [13], of which cough was the most common. Several studies show that mass screening using a cough-based strategy has moderate sensitivity [22, 24]. In this study, 81.3% of individuals with TB had at least 1 TB-related symptom, such that an algorithm beginning with symptom-screening would detect the majority of cases, while reducing the number of individuals who require testing. An additional 19 patients (8.8% of all cases) were detected by screening all individuals, irrespective of symptoms (Strategy 1); this required screening an additional 289 participants by Xpert, as most of the 3260 participants without symptoms also didn't produce sputum.

The high number of symptomatic participants may be due to the high frequency of smoking and illicit drug use in our population. Studies of the general population [25–27] show a lower prevalence of symptoms than studies with prison inmates [7, 22, 24]. Our study used cough of any duration as a symptom, rather than cough > 2 weeks as is commonly done in other studies, increasing sensitivity at the expense of specificity. Symptom-based screening in the context of mass screening may perform better in populations with a lower prevalence of smoking, in whom the specificity of cough is higher.

At the beginning of the study, we defined a CAD4TB threshold of ≥ 60 based on preliminary data indicating a sensitivity and specificity of approximately 80%. In this study, we found overall sensitivity to be 77.1% and specificity to be 82.8%. This sensitivity was slightly lower than that of symptom screening (81.3%), but specificity was much higher (60.5% for symptom screening). The cost of radiographic screening or

Table 2. Predictive Value of World Health Organization Tuberculosis Symptom Screen, Cough, and Computer-Aided Detection for Tuberculosis Score in 5387 Screened Inmates

Symptoms	Cough	CAD4TB Score	No. of Individuals (% of Total Cohort)	No. of Cases (TB Prevalence)	% of all TB Cases Detected
Absent	No	< 60	2793 (51.8)	7 (0.2)	3.3
		≥ 60	467 (8.7)	33 (7.0)	15.4
Total			3260 (60.5)	40 (1.2)	18.7
Present	No	< 60	498 (9.2)	6 (1.2)	2.8
		≥ 60	102 (2.0)	17 (16.6)	7.9
	Yes	< 60	1189 (22.0)	36 (3.0)	16.8
		≥ 60	338 (6.3)	115 (34.0)	53.8
Total			2127 (39.5)	174 (8.2)	81.3

Abbreviations: CAD4TB, Computer-Aided Detection for Tuberculosis; TB, tuberculosis.

Table 3. Total and Unit Cost for Each Screening or Diagnostic Procedure

Category		Total Cost of the Item, 2018 US\$	Unit Cost, 2018 US\$
Interview (n = 5387)			
Fixed costs	Equipment ^a	127.63	0.02
Variable costs	Human resources	10 027.80	1.86
	Inputs	105.21	0.02
Total		10 260.64	1.9
Clinical evaluation (n = 764)			
Variable costs	Human resources	1986.40	2.60
Total		1986.40	2.60
Radiograph (n = 5387)			
Fixed costs	Equipment ^a	9840.73	1.83
	CAD4TB software	667.00	0.12
	Transport mobile diagnostic unit	3875.96	0.72
Variable costs	Human resources	10 027.80	1.86
	CAD4TB score	9427.25	1.75
Total		33 838.74	6.28
Xpert MTB/RIF assay (n = 1743)			
Fixed costs	Equipment ^a	4954.98	2.84
	Maintenance	5167.95	2.97
Variable costs	Human resources	5013.90	2.87
	Inputs	18 339.23	10.52
Total		33 476.06	19.20

Abbreviations: CAD4TB, Computer-Aided Detection for Tuberculosis; MTB, *Mycobacterium tuberculosis*; RIF, rifampicin; US, United States.

^aProjected cost for a useful life of 10 years, based on the examinations made for 1 year.

symptom screening followed Xpert assay and CXR were considerably higher than that of symptom screening and Xpert for all individuals. The cost per case diagnosed for screening with Xpert assay for all individuals was lower. Alternative thresholds could be used to increase sensitivity of CXR with CAD4TB, at the expense of specificity, and further work is needed to identify optimal thresholds to maximize cost-effectiveness.

The strengths of our study include a representative sample of prisoners in Mato Grosso do Sul. The 3 prisons we screened

house 32% of the state's prison population [19, 21]. Our participation rate of 88.9% of the study's target population is similar to previous recruitments performed by our group [7] and other mass screening initiatives [19]. We undertook a rigorous microcosting analysis to derive "real-world" costs of implementing various components of triage and diagnosis in prisons, which are critical to decisions of scaling up systematic screening in these settings.

There are several limitations to this study. A major challenge was that only 27.2% of participants were able to produce a sputum sample in initial visit, and sputum induction was not possible in this setting. As a result, we likely underestimated the true prevalence of TB. However, our estimates for the yield and cost per case diagnosed when screening all participants reflect this limitation in prisons, which is not just a study challenge but a real-world obstacle to screening. While sputum induction would likely improve yield, it is possible that the efficiency (prevalence among tested individuals) would be lower, and the cost per case diagnosed would likely be higher. Our findings do, however, underscore the need for non-sputum-based diagnostics to reach patients earlier in the TB disease spectrum [28–31].

We do not use testing for TB infection, either through a interferon gamma release assays (IGRA) or tuberculin skin test, in our diagnostic algorithms. Previous tuberculin skin test conversion studies in Brazilian prisons have demonstrated hyperendemic rates of transmission with an annual conversion above 25% [7, 12]. In a setting with such a high force of infection, it is unclear how tuberculin skin (or IGRA) testing would accurately discriminate TB disease.

We estimated costs assuming that diagnostic infrastructure (Xpert machines, radiography equipment) was not present; for prisons in which such investments have been made for routine diagnostic purposes, incremental costs per case diagnosed via mass screening may be lower. Finally, we evaluated a limited combination of commonly used diagnostics (symptom screening, Xpert, radiography); while many more combinations

Table 4. Yield and Cost per Case Diagnosed for 4 Tuberculosis Screening Strategies

Strategies	Cases Diagnosed	Missed Cases	% Yield (95% CI)	Participants Screened With Xpert, No.	Mean Cost per Case Detected, US\$
All cases	214	485
Comparator groups					
Strategy 1: Sputum Xpert for all participants	160	54	74 (68–80)	1452	249
Strategy 2: Symptom screening If positive: Xpert	141	73	65 (59–71)	1163	255
Strategy 3: Chest radiography (CAD4TB) If score ≥60: Xpert	138	76	64 (57–70)	383	370
Strategy 4: Symptom screening If positive, Xpert If negative, CXR (CAD4TB) followed by Xpert if score ≥60	163	51	76 (70–81)	1248	395

Abbreviations: CAD4TB, Computer-Aided Detection for Tuberculosis; CI, confidence interval; CXR, chest radiograph; MTB, *Mycobacterium tuberculosis*; RIF, rifampicin; US, United States; Xpert, MTB/RIF assay.

or algorithms are possible using, for example, different criteria for interpretation of these screening tools, we selected these to be simple and scalable for use in resource-constrained settings.

In summary, our results suggest that mass TB screening in high-burden prisons, conducted by sputum Xpert testing of all inmates or those with symptoms, is an effective approach to case detection at a modest cost per case detected. Chest radiography, while it has higher overall accuracy than symptom screening, was more costly and did not substantially improve yield compared with sputum-based screening of all participants. Active case finding by sputum testing with Xpert MTB/RIF assay should be scaled up in Brazilian prisons and other high-burden countries to address TB in incarcerated populations.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. A. S. S., E. F. L., C. R., A. K., J. R. A., and J. C. were involved in the study conception and design. A. S. S., E. F. L., and F. L. were involved in the data collection. A. S. S., R. D. O., E. F. L., F. L., O. C., and L. M. were involved in the data analysis and manuscript drafting. C. G., T. C., A. K., J. R. A., and J. C. were involved in the study design and manuscript review. All authors read and approved the final manuscript.

Acknowledgments. The authors thank the State Health Department of Mato Grosso do Sul and State Agency of Administration Prisons for their full support during the study period; the study participants for their kind cooperation during the data collection process; and the Central Laboratory of the state of Mato Grosso do Sul for the support in the accomplishment of the laboratory tests. All data generated or analyzed during this study are included in this published article and its supplementary information files.

Disclaimer. All participants provided written informed consent prior to study participation. The study was approved by Federal University of Grande Dourados, the National Committee on Research Ethics (#2.195.047), and the Institutional Review Board and Stanford University (#40285).

Financial support. This study was supported by the US National Institutes of Health (grant number R01 AI130058).

Potential conflicts of interest. The authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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