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

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Brief Summary:

In this prospective study, we performed mass tuberculosis screening in Brazilian prisons and assessed yield, efficiency, and costs associated with various screening algorithms. We found that testing all participants with sputum Xpert MTB/RIF was sensitive and cost-efficient.

Abstract.

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

Methods: Between 2017 and 2018, inmates from the three prisons in Brazil were screened for tuberculosis by symptom assessment, chest radiography, sputum testing by Xpert MTB/RIF 4th generation and culture. Chest radiographs were scored by an automated interpretation algorithm (CAD4TB) that was locally calibrated to establish a positivity threshold. Four diagnostic algorithms were evaluated. We assessed the yield (percent 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 5,387 prisoners, of whom 214 (3.9%) were diagnosed with tuberculosis. Compared to other screening strategies initiated with radiography or chest symptoms, the trial of all participants with a single Xpert MTB / RIF sputum test detected 74% of all tuberculosis cases at a cost of $ 249. Performing Xpert MTB/RIF screening tests only on those with symptoms had a similar cost per case diagnosed (US$ 255) but missed as many cases (73 vs 54) as screening all inmates.

Conclusion: In this prospective study in three with prisons in high tuberculosis burden countries Brazilian prisons, we found that testing all participants with sputum Xpert MTB/RIF was sensitive approach, while remaining cost-efficient. These results support use of Xpert MTB/RIF for mass screening in tuberculosis-endemic prisons.

Keywords: Mass screening, tuberculosis, algorithms, prisons, cost-effectiveness.

INTRODUCTION

Tuberculosis 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 tuberculosis incidence by 90% by 2035 [2]. Despite an elevated focus on tuberculosis and increased funding, the tuberculosis burden is reducing by only 1–2% per year globally. To reach global targets, complementary interventions are needed to supplement current tuberculosis control. Recently, there has been a push to target interventions to populations with a high-burden of tuberculosis to reduce disease burden and transmission to the broader community [3, 4].

Prisons frequently have a very high burden of tuberculosis [5]. A meta-analysis of 19 studies found that the incidence of tuberculosis in prisons was 23 times greater than the surrounding population [5]. This high incidence leads to markedly elevated transmission rates. For example, three prisoner cohorts from Brazil, Colombia, and Iran have shown annual tuberculin conversion rates between 15 and 25% [6–8]. Effective case detection for tuberculosis in prisons is necessary to reduce ongoing transmission.

Despite the high rates of tuberculosis in prisoners and the potential importance of this population in the overall epidemic [3, 5, 9], there are few studies which have assessed the efficiency and costs of different approaches for screening for tuberculosis among incarcerated populations [7]. Studies reporting the yield of tuberculosis detected in prisons rarely compare distinct screening modalities or report their costs. Additionally, the use of sensitive molecular diagnostic tests, such as Xpert MTB/RIF, for tuberculosis screening among prisoners has not been widely explored. Studies using mathematical modeling suggest that annual mass screening can reduce the incidence of tuberculosis 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 tuberculosis. Our objective was to identify effective and efficient approaches to tuberculosis screening in prisons that could be implemented in low- and middle-income countries.

METHODS

Study Population

This study was carried out in three prisons in Mato Grosso do Sul, Brazil. Brazil's national prison population is over 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 (IPGC). These prisons exclusively incarcerate males ≥18 years old and were selected because they are the largest in the state and had the highest tuberculosis infection and disease rates in preliminary studies [7, 12].

Study procedures

All prisoners were invited to participate, and those who accept provided informed consent. 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). Each participant was then interviewed using a standardized questionnaire to collect demographic and clinical information. We asked each participant about tuberculosis-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 2ml. On this primary sample, Xpert MTB/RIF® (4th Generation) 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. Chest radiographs were then evaluated with Computer-Aided Detection for Tuberculosis (CAD4TB) version 5 [15]. The CAD4TB software assigns a quality assessment to a chest radiograph, 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 tuberculosis diagnosis. CAD4TB was calibrated with training data from X-ray images of participants with (n=80) and without (n=200) microbiologically confirmed tuberculosis. 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 re-evaluated; those who had been unable to produce sputum on the first occasion were given another opportunity and additionally coaching to produce a sample for testing by Xpert MTB/RIF. Those participants with negative results or who were still unable to produce sputum were assessed by a physician. All tuberculosis cases identified during screening were provided free treatment according to national guidelines [16].

Derivation of Mass Diagnostic Screening Algorithms

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

Strategy 1: Sputum testing by Xpert MTB/RIF for all participants who could produce sputum at the moment of questionnaire, regardless and presence of symptoms.

Strategy 2: Sputum testing by Xpert MTB/RIF only for those who reported any tuberculosis-related symptom of any duration and who could produce sputum at the moment of questionnaire.

Strategy 3: Chest radiography with CAD4TB scoring for all participants. Those with CAD4TB score ≥60 undergo sputum testing by Xpert MTB/RIF.

Strategy 4: Symptom screening, followed by sputum Xpert MTB/RIF testing for participants who reported a tuberculosis-related symptom. Those without any tuberculosis symptoms undergo chest radiography with CAD4TB scoring. Sputum collection and Xpert MTB/RIF testing was then offered to participants with a CAD4TB score ≥60.

Outcome Definitions

We followed national Brazilian guidelines and WHO definitions for tuberculosis diagnosis. We defined a tuberculosis case as any individual with a positive sputum Xpert MTB/RIF, sputum culture, or with a physician diagnosis based on clinical-epidemiological data and radiographic abnormalities. All participants with tuberculosis were administered a rapid 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 MTB/RIF, culture, radiographic and clinical evaluation. These costs include equipment, maintenance, consumables, and personnel time.

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 sold 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 MTB/RIF cartridge was $9.90 USD.

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 resources, inputs and evaluation of each X-ray 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 U.S. dollars using the quotation of 11/28/2018, being 3.87 R$ = 1.00 US$.

RESULTS

Study Population

Between November 2017 and July 2018, we screened 5,387 of 6,054 eligible study participants (88.9%). 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). Over 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. Over 71.4% of participants reported knowing a person diagnosed with tuberculosis, 8.9% reported having prior tuberculosis. During the study period, a total of 214 participants were diagnosed with pulmonary tuberculosis, equating to a prevalence of 3,973

per 100,000 participants (95% CI, 3,483-4,28). Disaggregating by prison, we identified tuberculosis prevalence of 5,567/100,000 (101/1,814) in EPJFC, 3,607/100,000 (82/2,273) in PED, and 2,384/100,000 (31/1,300) in IPCG.

Of the diagnosed cases on the visit initial, 172 (80.3%) were diagnosed by the Xpert MTB/RIF and sputum culture. At the initial visit, sputum was obtained from 1,467 inmates. Among these, Xpert MTB/RIF was performed on almost all participants (N=1,452, 98.9%) which detected 160 tuberculosis cases (Figure 2). Culture was performed on 1,385 participants and 12 additional cases were identified by culture. Sputum smear tests were performed on 1,386 participants; among the 214 TB cases who had smear microscopy performed, 49 (22.8%) had a positive smear. All tuberculosis cases that tested smear-positive were positive by Xpert MTB/RIF. Among 1,295 participants who were culture and/or Xpert MTB/RIF negative, 261 had a CAD4TB ≥60 score. According to the study protocol, these participants were re-evaluated for tuberculosis, 114 did Xpert MTB/RIF and, 22 were diagnosed (11 by Xpert MTB/RIF and 11 by clinical evaluation). Among participants who did not produce a sputum sample at the initial visit (N=3,919), 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 MTB/RIF positive. A further 11 cases were clinically diagnosed after physician re-evaluation. Among cases of active tuberculosis, 4 (1.9%) were HIV-positive.

Accuracy and Yield of Symptom- and Radiograph-based Screening

In the initial screening interview, 2,127 (39.5%) reported at least one WHO-defined tuberculosis symptom; the most common of the symptoms was cough (72.2%). Symptom screening alone had a sensitivity and specificity of 81.3% and 62.2%, 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 chest radiography with a CAD4TB score ≥60 was 77.1% and specificity was 82.8%.

The prevalence of tuberculosis 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 tuberculosis symptoms but CAD4TB score ≥60, comprising 8.9% of the cohort, was 6.8%. Among the 21.9% of participants with cough and CAD4TB score <60, prevalence was 3.0%. The highest risk group were participants with both cough and CAD4TB score ≥60, in whom prevalence was 33.1%; while only 6.4% of participants met both criteria, this accounted for 53.8% of all tuberculosis cases detected.

Costs and Efficiency of Screening Strategies

Among diagnostic modalities used during mass screening, the highest cost per participant was for Xpert MTB/RIF ($19.20 per participant), followed by chest radiography with CAD4TB scoring ($6.28 per participant), clinical evaluation ($2.60 per participant), and symptom screening interviews ($1.90 per participant) (Table 3). The costliest component of Xpert MTB/RIF were consumables (54.8%). For CAD4TB score chest radiography, human resources, equipment and CAD4TB score analysis contributed almost equally to main costs (29.6%, 29.1.0% and 29.8%, respectively).

The cost per case detected for all strategies ranged from $249 to $393 (Table 4). Strategy 1 (Xpert MTB/RIF for all participants) resulted in the highest yield, detecting 74% of all cases, at lowest cost ($249) per case detected. Strategy 2 (Xpert MTB/RIF for individuals with any symptom) had a low cost per case detected ($255) but resulted in lower yield (65%).

Strategies 3 and 4 had lower yield (73% and 78%) than Strategy 1 at a higher cost per case diagnosed ($331 and $384).

DISCUSSION

Tuberculosis is a major infectious disease problem within prisons worldwide. However, there is a dearth of evidence concerning how to effectively detect tuberculosis while controlling costs in these environments. As a result, screening modalities in prisons globally remain variable, with few high tuberculosis-burden countries enacting systematic screening policies in correctional facilities. In three prisons in Brazil, we found a very high prevalence (3,973 per 100,000) of tuberculosis through systematic screening of inmates. This prevalence is higher to the identified in other studies in prisons in Brazil and other countries [18–21].

The four strategies had similar yields. We found that systematic Xpert MTB/RIF testing among all individuals able to produce sputum was effective at a modest cost per case diagnosed of $249 dollars, and missing to detect 10 fewer cases compared to strategy 4. Implementing a symptom screen to identify individuals for sputum testing had a similar efficiency at US$255 per case detected. Strategies involving chest radiography were most costly and did not increase the overall yield compared with sputum Xpert MTB/RIF testing alone. Together, these results suggest that testing all inmates able to produce sputum using Xpert MTB/RIF 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 39.4% of all inmates reported at least one WHO-defined tuberculosis 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 tuberculosis had at least one tuberculosis-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 29 patients (13.6% of all cases) were detected by screening all individuals, irrespective of symptoms; this required screening an additional 446 participants by Xpert MTB/RIF, as most of the 3,260 participants without symptoms also didn't produce sputum. While symptom-based screening was the most efficient algorithm, screening everyone who could produce sputum identified more cases at comparable costs per case detected.

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 triage 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 X-ray screening was considerably higher than that of symptom screening, and the cost per-cased diagnosed for symptom screening followed by Xpert MTB/RIF was lower. Alternative thresholds could be used to increase sensitivity of

chest radiography 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 three 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 tuberculosis. However, our estimates for the yield and cost per case diagnosed when screening all participants reflects 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 tuberculosis disease spectrum [28–31].

We do not use testing for tuberculosis infection, either through a Quantiferon 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's unclear how tuberculin skin (or Quantiferon) testing would accurately discriminate tuberculosis disease.

We estimated costs assuming that diagnostic infrastructure (Xpert MTB/RIF 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 MTB/RIF, radiography); while many more combinations 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.

CONCLUSIONS

In conclusion, our results suggest that mass tuberculosis screening in high-burden prisons, conducted by sputum Xpert MTB/RIF 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 improve yield compared with sputum-based screening of all participants. Active case finding by sputum testing with Xpert MTB/RIF should be scaled in Brazilian prisons and other high-burden countries to address the tuberculosis in incarcerated populations.

Notes

Author Contributions:

ASS, EFL, CR, AK, JRA and JC were involved in the study conception and design. ASS, EFL and FL were involved in the data collection. ASS, RDO, EFL, FL, OC and LM were involved in the data analysis, and manuscript drafting. CG, AC, AK, JRA and JC were involved in the study design and manuscript review. All authors read and approved the final manuscript.

Acknowledgments

We thank the State Agency of Administration Prisons (AGEPEN) for their full support during the study period, the study participants for their kind cooperation during the data collection process, and the Central Laboratory (LACEN) of the state of Mato Grosso do Sul for the support in the accomplishment of the laboratory tests. 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). All data generated or analysed during this study are included in this published article and its supplementary information files.

Funding: This study was supported by grants from the National Institutes of Health (R01 AI130058) and State Secretary of Health of Mato Grosso do Sul.

Competing interests: The authors declare that they have no competing interests

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Table 1. Sociodemographic characteristics and risk factors for tuberculosis among screened inmates.

Variables	Total (N=5,387) n (%)	TB cases (N=214) n (%)	No TB (N=5,173) n (%)	*P* Value
Prison unit				
PED	2,272 (42.2)	82 (38.3)	2,191 (42.4)	0.24
EPJFC	1,814 (33.7)	101 (47.2)	1,713 (33.1)	<0.01
IPCG	1,300 (24.1)	31 (14.5)	1,269 (24.5)	<0.01
Median age [IQR]	30.5 [25, 37]	30 [25, 37]	31 [25, 37]	<0.01
Ethnic				
Mixed	3,312 (61.5)	136 (63.6)	3,176 (61.3)	0.52
White	1,306 (24.2)	49 (22.9)	1,257 (24.3)	0.64
Black	617 (11.5)	23 (10.7)	593 (11.4)	0.76
Indigenous	144 (2.6)	6 (2.8)	138 (2.6)	>0.99
Asian	8 (0.1)	0 (0.0)	8 (0.2)	>0.99
Less than 8 years of schooling	3,540 (65.7)	154 (72.0)	3,386 (65.4)	0.04
Current smoker	3,139 (58.3)	161 (75.2)	2,978 (57.5)	<0.01
Illicit drug use over the last year	3,172 (58.8)	169 (78.9)	3,003 (58.0)	<0.01
BCG vaccinated	4,736 (87.9)	185 (86.4)	4,551 (87.9)	0.49
Previous TB	482 (8.2)	56 (26.2)	426 (8.2)	<0.01
Know someone with TB	3,849 (71.4)	181 (84.6)	3,668	<0.01

			(70.9)	
Report any WHO TB symptoms	2,127 (39.4)	174 (81.3)	1,953 (37.7)	<0.01
Report cough	1,527 (28.3)	151 (70.6)	1,376 (26.6)	<0.01
Previously incarcerated	3,786 (70.3)	167 (78.0)	3,619 (70.0)	<0.01

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

Table 2. Predictive value of WHO symptom screen, cough and CAD4TB score for tuberculosis in 5,387 screened inmates.

Symptoms	Cough	CAD4TB Score	Number of individuals (% of total cohort)	Number of cases (TB prevalence)	% of all TB cases detected
Absent	No	<60	2,793 (51.8)	7 (0.2)	3.3
		≥60	467 (8.7)	33 (7.0)	15.4
	Total		3,260 (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	1,189 (22.0)	36 (3.0)	16.8
		≥60	338 (6.3)	115 (34.0)	53.8
	Total		2,127 (39.5)	174 (8.2)	81.3

Table 3. Total and unit cost for each screening or diagnostic procedure.

	Category	Total cost of the item (2018 USD)	Unit cost (2018 USD)
Interview (N = 5,387)			
Fixed Costs	Equipment[§]	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	1,986.40	2.60
Total		1,986.40	**2.60**
X-Ray (N = 5,387)			
Fixed Costs	Equipment[§]	9,840.73	1.83
	CAD4TB Software	667.00	0.12
	Transport mobile diagnostic unit	3,875.96	0.72
Variable Costs	Human Resources	10,027.80	1.86
	CAD4TB Score	9,427.25	1.75
Total		**33,838.74**	**6.28**
Xpert MTB/RIF (N = 1,743)			
Fixed Costs	Equipment[§]	4,954.98	2.84

	Maintenance	5,167.95	2.97
Variable Costs	Human Resources	5,013.90	2.87
	Inputs	18,339.23	10.52
Total		**33,476.06**	**19.20**

USD: United States Dollars

[§]Projected cost for a useful life of 10 years, based on the examinations made for 1 year.

Table 4. Yield and cost per case diagnosed for four tuberculosis screening strategies.

Strategies	Cases Diagnosed	Missed Cases	% Yield (95% CI)	No. Participants Screened with Xpert MTB/RIF (%)	Mean Cost* (US$) per case detected
All cases	214	–	–	–	485
Comparator Groups					
Strategy 1: Sputum Xpert MTB/RIF for all participants	160	54	74 (68-80)	1,452	249
Strategy 2: Symptom screening: If Positive: Xpert MTB/RIF	141	73	65 (59-71)	1,163	255
Strategy 3: Chest Radiography (CAD4TB) If score ≥60: Xpert MTB/RIF	158	56	73 (67-79)	538	336
Strategy 4: Symptom screening: If Positive, Xpert MTB/RIF If Negative, Chest Radiography (CAD4TB) followed by Xpert MTB/RIF if score ≥60	169	45	78 (73-83)	1,407	393

Figure Legends

Figure 1. Outline of tuberculosis screening strategies assessed among prisoners in the study.

Figure 2. Tuberculosis cases overlap of screening strategies. Strategy 1: Xpert MTB/RIF test for all prisoners. Strategy 2: Xpert MTB/RIF test only for those who reported any TB symptom. Strategy 3: Chest radiography, those with CAD4TB score ≥60 undergo Xpert MTB/RIF test. Strategy 4: Symptom screening, followed by Xpert MTB/RIF test, those without any tuberculosis symptoms undergo chest radiography with CAD4TB scoring followed by Xpert MTB/RIF test.

Figure 1

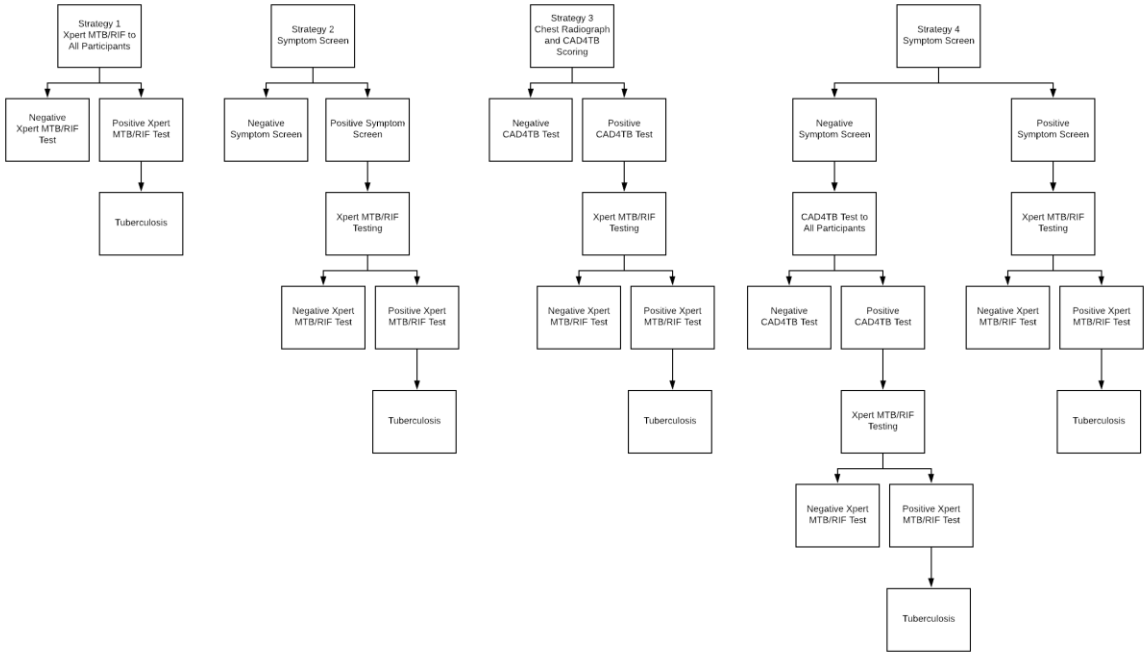

Figure 2