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What Is the Optimal Community-Based Tuberculosis Screening Algorithm for People Who Inject Drugs in a High-Burden Setting?

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Background. Although people who inject drugs (PWID) are a high-risk group for tuberculosis (TB), current case-finding strategies fail to identify most TB cases. There is a need for an optimized community-based algorithm to improve TB detection in such disproportionately affected populations.

Methods. Using respondent-driven sampling, we recruited PWID at community sites in Hai Phong, Vietnam, screening for classic TB symptoms, C-reactive protein blood measurement, portable on-site chest x-ray with CAD4TB software (Computer-Aided Detection for Tuberculosis version 7; Delft Imaging Systems BV), and Xpert MTB/RIF on sputum. Any participants suspected of TB by on-site physicians were referred to the infectious disease hospital for confirmatory testing, and external experts validated final diagnoses, which were then used as the TB gold standard. We aimed to identify the screening algorithm with the highest case detection at the lowest cost among different on-site testing combinations. Ingredients-based costing was used to evaluate the cost per test and cost per case detected for each algorithm.

Results. Among the 1080 PWID enrolled, 47 (4.4%; 95% CI, 2.8%–6.4%) were diagnosed with TB disease. When compared with the current symptom-based TB screening strategy in Vietnam (double D), systematic chest x-ray with CAD4TB, Xpert MTB/RIF for those with CAD4TB ≥50, and referral to care for those with either CAD4TB ≥70 or a positive Xpert test result doubled the sensitivity (82.9% vs 43.9%) and yield (3.2% vs 1.7%) while maintaining a reasonable cost per TB case detected (US $439 vs $309 for standard of care).

Conclusions. We defined an acceptable and moderate cost algorithm that improves efficiency for community-based TB screening among PWID in Vietnam. To reflect real TB prevalence, we make the case that active case finding and systematic screening strategies should not limit testing to those with a positive symptom screen.

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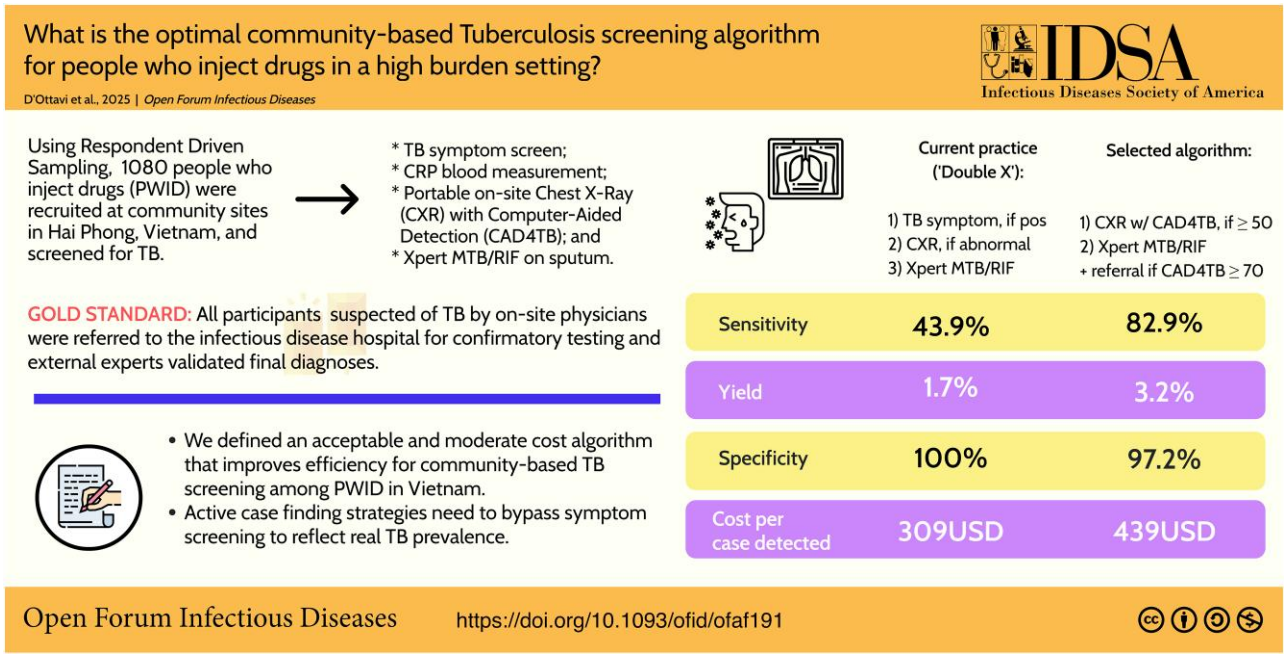
Graphical Abstract



This graphical abstract is also available at Tidbit: https://tidbitapp.io/tidbits/what-is-the-optimal-community-based-tuberculosis-screening-algorithm-for-people-who-inject-drugs-in-a-high-burden-setting-b6c6c834-4f3d-46ff-b917-5f5a2951f698?utm_campaign=tidbitlinkshare&utm_source=IO

Keywords. community-based approaches; cost-efficiency; people who use drugs; subclinical tuberculosis; tuberculosis screening.

Despite national and international efforts to reach its elimination, there are >10 million new cases of tuberculosis (TB) annually [1]. Although the World Health Organization (WHO) End TB milestones set in 2015 for 2025 include a 50% reduction in global TB incidence, by the end of 2022, only an 8.7% reduction had been achieved [1].

Vietnam is one of the WHO's 30 high TB burden countries, with an estimated prevalence of 322 cases per 100 000 adults (0.32%) [2], as well as 1 of the 10 countries with the highest rates of undiagnosed TB [1]. In 2020, it was estimated that only 58% of incident TB cases were diagnosed and notified to the Vietnamese National Tuberculosis Programme [3, 4]. To reduce TB incidence as outlined by the End TB program, testing efficacy and coverage must improve to find these missing cases through strategies that optimize performance and cost. Recent increases in allocations by the Global Fund to the Vietnam National Tuberculosis Programme aim to scale up active case-finding strategies [4], notably targeting high-risk groups via community-based organizations (CBOs) and peer educator involvement following the HIV model, which proved very effective in Vietnam [5].

Systematic screening and active case finding for TB are recommended by the WHO, especially for high-risk groups, referred to as *intensified case finding*. The WHO recognizes a number of high-risk groups for TB, including people who inject drugs (PWID) [1, 6]. A previous community-based study among PWID in Vietnam found an alarming TB prevalence of 2.2%, which was likely underestimated [7]. There is sparse epidemiologic data for TB disease among PWID, but a recent review found TB prevalence estimates up to 10% among PWID and 35% among PWID with HIV [8]. However, PWID are seldom targeted for screening, treatment, or surveillance strategies by national tuberculosis programs. PWID also face specific obstacles regarding diagnosis and linkage to care, including simultaneous health issues, stigma and discrimination enabling health care avoidance, and poor awareness of TB disease and inaccurate symptom recognition [9]. These social and structural barriers to care render traditional TB screening strategies inefficient for this key population, as chest x-ray (CXR), sputum collection, and turnaround times for result delivery usually require multiple health center attendances. A PWID-specific, fully community-based screening strategy should be envisioned to detect as many TB cases as possible and connect this otherwise marginalized population to care.

The current systematic screening strategy adopted in Vietnam is the locally dubbed "double D" strategy [10, 11] and the WHO's A.1.7, "Sequential positive serial screening with any TB symptom and CXR" [12]. It consists of a 3-step cascade: (1) the WHO-recommended 4 symptom screen; (2) if symptomatic, CXR; and (3) if abnormal, sputum collection for Xpert MTB/RIF, with treatment initiation for those with a positive Xpert result and with no further confirmatory testing for those with a negative Xpert result. WHO guidelines for

systematic screening in high-risk groups [12] rely on TB symptoms as a first triage step, even though many recent studies showed that up to half of TB cases may be completely asymptomatic and infectious prior to the onset of symptoms [13–16]. In fact, screening interventions in high-incidence settings (largely symptom based) have been unable to significantly affect TB transmission dynamics at the population level, as evidenced by the very moderate progress toward WHO End TB targets, with asymptomatic TB likely being a major driver of TB transmission in high-burden populations [17, 18].

Many studies have demonstrated that community-based active case-finding strategies effectively improve TB case finding [19–21] and can have a substantial and sustained impact on TB prevalence. One cluster-randomized trial showed a 64% decrease in TB prevalence in 4 years as a result of community-wide screening through Xpert MTB/RIF on sputum, regardless of symptoms [22]. However, low-complexity community-based intensified case-finding strategies for TB, especially in specific populations such as PWID, remain ill-defined and often costly [23–28]. The WHO End TB recommended target for systematic screening tools is >90% sensitivity and >70% specificity, but very few of the evaluated strategies in the latest WHO report met these criteria [12]. There is an urgent need for screening strategies that meet the WHO criteria and for practical ground-level considerations, such as cost-efficiency, social barriers to care, and acceptability, based on a fully community-based approach for intensified case finding.

The aim of this work was to identify an algorithm for community-based TB screening among PWID in Vietnam that is acceptable, efficient in terms of yield and sensitivity, and moderately cost.

MATERIALS AND METHODS

Study Design, Setting, and Population

This work was part of an ongoing larger interventional study entitled Drug Use and Infections in Vietnam–Tuberculosis (DRIVE-TB; NCT05655702). We recruited PWID to be screened for TB in Hai Phong, Vietnam, using respondent-driven sampling (RDS) surveys, which provide robust epidemiologic data and are designed for hard-to-reach populations. Twenty initial "seeds" were selected to ensure the representation of gender, age, HIV status, and other important characteristics of the PWID population. Each seed first participated in study procedures and then was given 3 coupons to distribute to potentially eligible participants. Persons presenting coupons at the community site were invited to participate in the study; after participating, they were given coupons to recruit new participants. RDS recruiting continued until the target sample size was reached (N = 1000).

All study procedures took place at 2 community sites, with CBO and peer educator involvement in recruitment, TB information dissemination, and sample collection. Eligibility criteria included being at least 18 years of age, injection drug use confirmed by presence of heroin or methamphetamine in urine and recent injection marks, and ability to provide informed consent. Participants were excluded from this analysis if they were currently receiving TB treatment at the time of screening. For the purpose of this analysis, pregnant women were also excluded due to their ineligibility for CXR in Vietnam.

Data Collection

A structured interview was administered by trained CBO interviewers to collect declarative information related to sociodemographic characteristics, drug injection practices, and any history of TB disease. WHO-recommended TB symptoms were evaluated at the end of the interview and include persistent fever, cough, night sweats, and weight loss.

Sample Collection and TB Case Confirmation

In addition to evaluation of TB symptoms, all participants underwent a full panel of triage tests: C-reactive protein (CRP) concentration, CXR with computer-aided detection for TB, and Xpert MTB/RIF Ultra on sputum samples. Venous blood samples were collected in 3-mL EDTA tubes for CRP serum level with the DXC 700 AU Clinical Chemistry System (Beckman Coulter). CXR was done on-site by portable x-ray machines (FDR Xair XD2000; Fujifilm Corporation), and images were digitalized and interpreted by CAD4TB software (Computer-Aided Detection for Tuberculosis version 7; Delft Imaging Systems BV). Trained staff from CBOs organized sputum collection on-site and sent samples for Xpert MTB/RIF Ultra assay to a central university laboratory.

To detect all TB cases among participants, on-site study physicians referred any participants suspected of TB to the infectious disease department of the local tertiary-level referral hospital (Viet Tiep Hospital) for further case investigation and supplementary examinations, including bronchoscopies with bronchoalveolar lavage and mycobacteria growth indicator tube culture, additional Xpert MTB/RIF Ultra testing, or computed tomography scan when needed. Suspicion of TB was based on any of the following: sputum Xpert trace result, Xpert negative result and clinical symptoms compatible with TB, CRP >50, or CXR compatible with TB according to CAD4TB >50 or physician reading. Participants with a positive Xpert result were referred to local TB units to initiate treatment, per routine care in Vietnam. All referrals benefited from individual case management and assistance from CBO members. All TB diagnostic decisions of the local infectious diseases physicians (negative or positive) were then validated by an adjudication committee composed of experienced local and international TB clinicians, and culture was done for all presumed cases.

The gold standard for TB used in this analysis was the outcome of the international TB expert adjudication committee.

Statistical Analysis

RDS validation indicators were checked to ensure that the sample was representative and unbiased [29, 30]. TB prevalence was estimated with a 95% CI and adjusted to account for RDS recruitment design [29]. Sociodemographic variables were described for the study population overall and by final TB diagnosis.

Determination of the Screening Algorithm and Performance Measures

The discriminatory capacity of each of the 4 tests (TB symptoms, CRP, CXR, and Xpert) was evaluated by receiver operating characteristic analysis, and optimal threshold values were calculated with the Youden index. Optimal thresholds were calculated for the study population as a whole, as well as within subgroups of the potential screening algorithms when pertinent. Sensitivity analyses were done for whether user-friendly thresholds (ie, optimal thresholds rounded to nearest tens) affected performance.

Combining the results from individual triage test performance, receiver operating characteristic analyses, classification and regression tree (CART) analyses with feasibility considerations, we determined the most high-performing candidate algorithms to retrospectively evaluate against the double D reference algorithm. Participants with confirmed TB disease after adjudication are herein referred to as "true" cases. For each algorithm, participants who would be referred to health care services for treatment or further investigation are referred to as cases "detected" by the algorithm. Participants with missing test results were included in analyses, with missing results considered dropouts and classified as negative at that test node and with no test costs applied.

Each algorithm was evaluated through multiple performance outcomes: yield, sensitivity, positive predictive value (PPV), and specificity. Note that yield is defined as the proportion of true cases detected by the algorithm among all included participants.

Cost Analyses

We used an ingredients-based approach whereby we identified and valued each required resource for each type of test [31, 32]. The costs account for equipment and their maintenance, consumables, generated waste, and personnel time. The costs do not account for any research or recruitment costs. For equipment and consumables that were acquired or rented for research purposes but did not reflect the real purchase or rental costs in Vietnam, costs were estimated from the Global Fund and Stop TB lists of subsidized prices to reflect real local costs. Equipment was estimated to have a life span of 10 years and depreciated linearly [33]. All costs were calculated in Vietnamese dong and presented in 2024 US dollars.

For each algorithm, we calculated the total cost per algorithm and cost per true case detected. Incremental cost-effectiveness ratios were calculated by the current double D strategy as the counterfactual strategy, with the number of additional cases detected as a measure of model benefit, to identify algorithms that maximized the number of true cases that could be detected per increase in costs [31]. A theoretical efficiency frontier approach was used to compare the different models and select the optimized algorithm [34].

All statistical analyses were carried out in Stata version 16.1 (Stata Corp) and RStudio version 4.2.2 (Posit Software, PBC).

Patient Consent Statement

The present study was approved by the Hai Phong University of Medicine and Pharmacy institutional review board (07/IRB_HPMU) and the Ministry of Health. All included participants signed an informed consent form at enrollment. All procedures were carried out in accordance with relevant guidelines and regulations.

RESULTS

Study Population

Between 2 October 2023 and 28 November 2023, 1080 PWID were enrolled in the study, and RDS sample validity indicators were met: equilibria were reached after 2 to 3 waves, and homophilies were low for all major variables. The 1080 participants had a median age of 45 years (IQR, 39–52), and 95% were men (Supplementary Table 1). Half (53.8%) had been injecting heroin for over 15 years; half (53.8%) were receiving methadone maintenance treatment at the time of screening; and 23.3% were HIV positive. In addition, 13.9% of participants reported a history of TB disease in their lifetime.

Participants widely accepted TB screening, with only 3 missing results for CXR and with sputum samples collected for 98.9% (12 participants could not produce sputum). TB was confirmed for 47 PWID for an overall weighted prevalence of 4.4% (95% CI, 2.8%–6.4%; Figure 1). Of these, 5 were receiving TB treatment at the time of screening, and 1 with extrapulmonary TB was already being treated by the Hai Phong military hospital. Two pregnant women were also excluded from this analysis, as was 1 participant for whom TB was not confirmed at the time of screening per the study gold standard but who was undergoing TB treatment.

A description of the participants included in this analysis is provided in Table 1. Confirmed TB cases were different from those that were TB negative, notably with a significantly lower median body mass index.

Performance of Each Triage Test

Results of each triage test differed significantly between confirmed true TB cases and TB-negative cases (Table 1). TB symptoms showed low sensitivity, with 41.5% of confirmed cases not declaring any TB symptoms. Xpert on sputum was 75.6% sensitive and highly precise (96.9%) with 99.9% specificity (Supplementary Table 2). The optimal threshold obtained for CRP concentration was 1.65 mg/L, conferring 73% sensitivity and 6.2% PPV with 56% specificity. The optimal threshold for CXR abnormality was

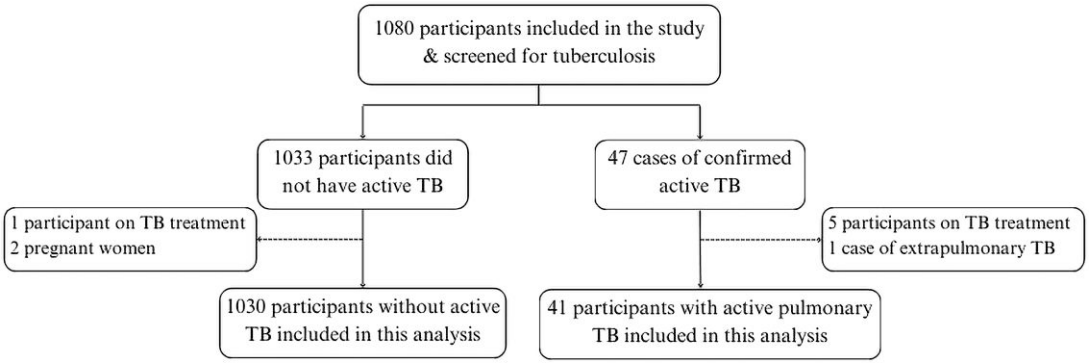


Figure 1. Participant flowchart. Abbreviation: TB, tuberculosis.

a CAD4TB likelihood of 51.5, yielding 88% sensitivity and 30.3% PPV with 92% specificity (Supplementary Figures 1 and 2).

Evaluation of Current Strategy

The double D screening strategy was retrospectively evaluated, and 366 (34.1%) participants were symptomatic. Of these, 57 (15.6%) had abnormal CXR results (CAD4TB ≥50), of which 18 (31.6%) had a positive Xpert result. With this strategy, we would have obtained 43.9% sensitivity, 1.7% yield, and 100% PPV and specificity (Table 2).

Choice and Performance of Candidate Screening Algorithms

After CART analysis (Supplementary Figure 3) and feasibility considerations, the highest performing candidate algorithms were as follows (Figure 2):

Algorithm 1: TB symptom screen and CXR for all participants and Xpert on sputum for those with at least 1 TB symptom or abnormal CXR result (WHO A.1.6, "Parallel screening with any TB symptom and CXR" [12]).

Algorithm 2: CXR for all participants and Xpert on sputum for those with abnormal CXR result (WHO 2013 reference 3b with the addition of CAD4TB software [35]).

Algorithm 3: CXR and Xpert for all participants.

For algorithms 1 and 2, sensitivity analyses showed no difference with the optimal CAD4TB threshold (51.5) vs a friendlier threshold of 50, so the abnormality threshold was set at 50 (Supplementary Table 2). The third algorithm was originally proposed by the CART analysis, with a first node splitting participants by Xpert result, followed by CXR among Xpert-negative cases, for whom the optimal threshold was a CAD4TB likelihood ≥70, highly suggestive of TB disease (Supplementary Figure 3). Since using Xpert as a first classification node would require patients to return to screening sites another time for sputum results (increasing risk of dropouts and diagnostic waiting times), we designed a more pragmatic algorithm with the 2 tests done simultaneously (algorithm 3; sensitivity analysis in Supplementary Table 3).

Among the 3 candidates, algorithm 1 was most precise (96.6% of detected cases were true cases), and algorithm 3 had the highest yield and sensitivity (3.5% and 92.7%, respectively) and was the only candidate to meet the WHO screening targets (Table 2). Algorithm 2 also stood out, with 3.2% yield and 82.9% sensitivity, though only 54% precise.

Cost Evaluation

Among the triage tests, Xpert on sputum was most expensive (US $33.44 per person screened), followed by mobile CXR (US $10.01 per person), CRP (US $4.79 per person), and TB symptom screen, which was a quasi-negligible fraction of US $1 per person screened (Supplementary Table 2). The cost per case detected for the different screening algorithms ranged from US $309.3 for double D to $1213.4 for algorithm 3 (Table 2).

Based on the current double D strategy as a counterfactual, the incremental costs for each additional case detected ranged from US $585.9 for algorithm 2 to US $2026.6 for algorithm 3 (Table 2). The theoretical efficiency frontier plot (Figure 3) establishes algorithm 2 as the dominant screening strategy, optimizing performance and cost. Exploratory analyses regarding acceptability of costs were performed via a cost-effectiveness acceptability curve and estimated willingness-to-pay threshold. These showed that algorithm 2 is quickly much more likely to be cost-effective with respect to the current double D and remains the most cost-effective until willingness to pay becomes quite high, at which point algorithms 2 and 3 are equally as likely to be cost-effective (Supplementary Figure 4). To account for the potential health care surcharge as a result of poor algorithm PPV, we performed a sensitivity analysis using a rough worst-case scenario estimate of additional TB diagnostic confirmation costs obtained from the local referral hospital for those referred without a positive result for Xpert on sputum (data not shown). Although the costs increased, no drastic difference in algorithm dominance was exhibited.

Table 1. Participant Characteristics and Triage Tests by Final TB Diagnosis

	Median (IQR) or No. (%)			
	All (n = 1071)	TB Negative (n = 1030)	True TB Cases (n = 41)	*P* Value
Sociodemographic characteristics				
Age, y	45 (39–52)	45 (39–52)	47 (42–54)	.075[a]
Gender				.283[b]
Male	1020 (95.2)	979 (95.1)	41 (100.0)	
Female	50 (4.7)	50 (4.9)	0 (0.0)	
Transgender	1 (0.1)	1 (0.1)	0 (0.0)	
Body mass index,[c] kg/m^2	20.5 (18.8–22.6)	20.6 (18.9–22.7)	19.6 (17.6–20.5)	<.001[a]
Tobacco				.538
Never or ceased	148 (13.8)	141 (13.7)	7 (17.1)	
Current smoker	923 (86.2)	889 (86.3)	34 (82.9)	
Years injecting heroin[d]				.328
<5	134 (12.5)	132 (12.8)	2 (4.9)	
5 to <10	134 (12.5)	130 (12.6)	4 (9.8)	
10 to <15	226 (21.1)	218 (21.2)	8 (19.5)	
≥15	576 (53.8)	549 (53.4)	27 (65.9)	
Currently undergoing MMT[e]	573 (53.6)	553 (53.8)	20 (48.8)	.528
Ever been incarcerated[f]	729 (68.1)	700 (68.0)	29 (70.7)	.709
Ever been to prison	436 (40.7)	412 (40.0)	24 (58.5)	.018
Ever been to rehabilitation center	526 (49.1)	509 (49.4)	17 (41.5)	.318
HIV positive	251 (23.4)	240 (23.3)	11 (26.8)	.601
Currently undergoing ART	236/245 (96.3)	225/234 (96.2)	11/11 (100.0)	>.99[b]
Viral load >1000 copies/mL	33/250 (13.2)	30/239 (12.6)	3/11 (27.3)	.165[b]
History of TB	146 (13.6)	134 (13.0)	12 (29.3)	.003
Triage test				
At least 1 TB symptom[g]	366 (34.2)	342 (33.2)	24 (58.5)	.001
Cough	163 (15.2)	150 (14.6)	13 (31.7)	.003
Fever	39 (3.6)	33 (3.2)	6 (14.6)	<.001
Night sweats	106 (9.9)	96 (9.3)	10 (24.4)	.002
Weight loss	241 (22.5)	224 (21.8)	17 (41.5)	.003
CRP result				
mg/L	1.4 (0.5–3.6)[d]	1.3 (0.5–3.4)[d]	2.6 (1.3–6.7)	.002[a]
≥1.65 mg/L	486 (45.4)[d]	456 (44.3)[d]	30 (73.2)	<.001
CXR CAD4TB				
Likelihood score	29 (17–38)[h]	28 (16–37)[h]	72 (59–78)	<.001[a]
Score ≥51.5	119 (11.1)[h]	83 (8.1)[h]	36 (87.8)	<.001
Xpert positive on sputum	32 (3.0)	1 (0.1)	31 (75.6)	<.001

Statistical comparisons were performed by Pearson χ^2 test for categorical variables.

Abbreviations: ART, antiretroviral therapy; CAD4TB, Computer-Aided Detection for Tuberculosis (software); CRP, C-reactive protein; CXR, chest x-ray; MMT, methadone maintenance treatment; TB, tuberculosis.

[a] *P* value obtained by Wilcoxon rank sum test for continuous variables.

[b] *P* value obtained by Fisher exact test when conditions were not met for Pearson χ^2 test.

[c] Body mass index was calculated using measured weight and height by study staff, and is not self-reported.

[d] 1 missing value.

[e] 2 missing values.

[f] Incarceration encompasses any detainment in prison, rehabilitation centers, and/or short-term detention facilities.

[g] TB symptoms include persisting fever, cough, night sweats, and recent weight loss at the time of interview, per World Health Organization–recommended 4-symptom screen.

[h] 3 missing values.

Sociodemographic and clinical TB-related characteristics of the correctly classified true cases and misclassified cases (false negatives and false positives) for algorithm 2 are presented in Supplementary Table 4. Of particular interest, about 76% of wrongly referred cases declared a history of TB disease and are likely to experience post-TB lung damage.

DISCUSSION

Analysis of 1071 test results from PWID in Vietnam identified a community-based screening algorithm for TB that improves the effectiveness of triage screening at a moderate additional cost. This strategy, based on algorithm 2, consists of providing CXR for everyone, followed by Xpert on sputum for those with

Table 2. Performance and Cost per Case Detected for Each Screening Algorithm

	Double D	Algorithm 1	Algorithm 2	Algorithm 3
No.				
True positives of 41 TB cases	18	28	34	38
False positives	0	1	29	29
True negatives	1030	1029	1001	1001
False negatives	23	13	7	3
% (95% CI)				
Yield	1.7 (0.9–2.4)	2.6 (1.6–3.6)	3.2 (2.1–4.2)	3.5 (2.4–4.7)
Sensitivity	43.9 (43.4–44.4)	68.3 (67.8–68.7)	82.9 (82.6–83.3)	92.7 (92.4–92.9)
Specificity	100	99.9 (99.9–99.9)	97.2 (97.2–97.2)	97.2 (97.2–97.2)
PPV	100	96.6 (96.3–96.8)	54.0 (53.6–54.3)	56.7 (56.3–57.1)
NPV	97.8 (97.8–97.8)	98.8 (98.7–98.8)	99.3 (99.3–99.3)	99.7 (99.7–99.7)
US $				
Total cost	5568.14	25 165.88	14 932.82	46 100.17
Cost per case detected	309.34	898.78	439.20	1213.16
ICER	…	1959.77	585.29	2026.60

Abbreviations: ICER, incremental cost-effectiveness ratio; PPV, positive predictive value; TB, tuberculosis.

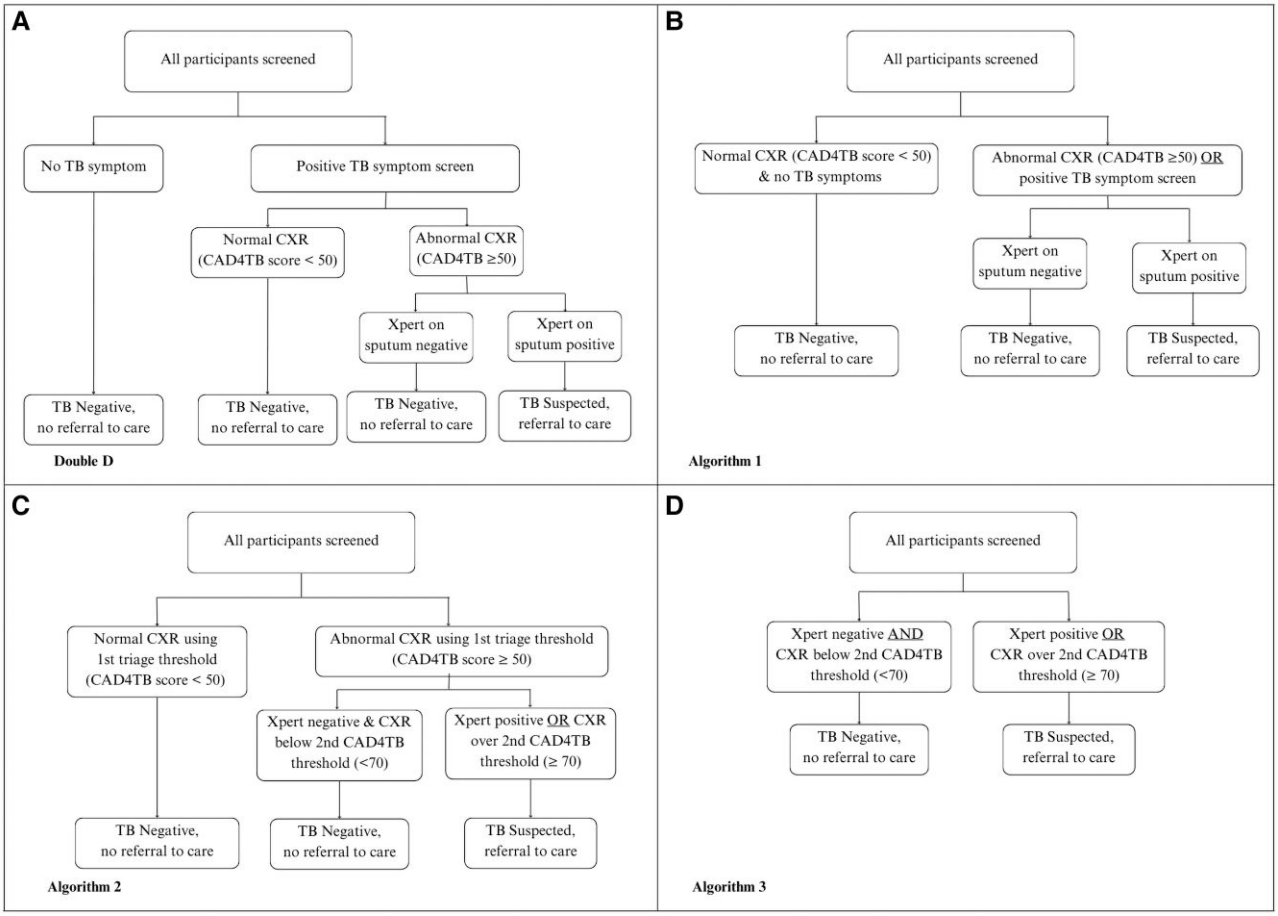


Figure 2. Depiction of the 4 retrospectively evaluated candidate screening algorithms. (A) Double D Algorithm: WHO-recommended four symptom screen, and if symptomatic, CXR and if abnormal, sputum collection for Xpert MTB/RIF Ultra. (B) Algorithm 1: TB symptom screen and CXR with CAD4TB for all participants, and Xpert on sputum for those with at least 1 TB symptom or abnormal CXR. (C) Algorithm 2: CXR with CAD4TB for all participants, and Xpert on sputum for those with abnormal CXR. (D) Algorithm 3: CXR with CAD4TB and Xpert for all participants. Abbreviations: CAD4TB, Computer-Aided Detection for Tuberculosis (software); CXR, chest x-ray; TB, tuberculosis.

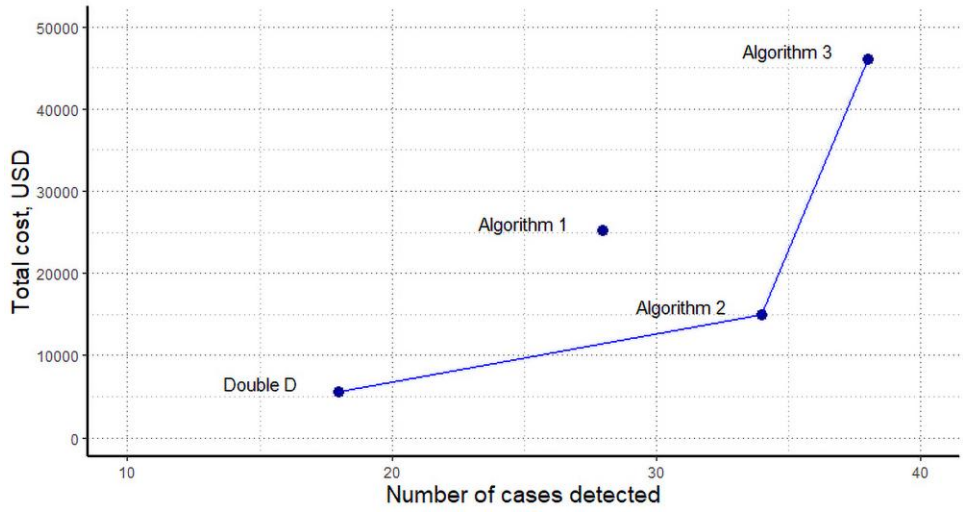


Figure 3. Theoretical efficiency frontier plot for optimized tuberculosis case detection as compared with the current double D strategy. Abbreviation: USD, United States dollar.

TB likelihood ≥50 from CAD4TB software and a referral to care for all those with either a TB likelihood ≥70 or a positive Xpert result. This algorithm doubled the performance of the current screening strategy (sensitivity and yield), all while maintaining a reasonable cost per case detected (US $439.20 vs $309.34 [double D]). Although algorithm 3 (Xpert and CXR for all participants) was the only candidate to meet the WHO targets (>90% sensitivity and >70% specificity), it comes at a much higher cost per case detected and is not likely to be as cost-effective as algorithm 2, unless willingness to pay is quite high.

Early diagnosis of all persons with TB disease can have important implications for potentially reducing onward transmission, which is necessary to achieve the WHO targets for reduced TB incidence. A strategy similar to algorithm 2 was effectively used for household contacts of TB-confirmed cases in Haiphong and Quang Nam cities, Vietnam [11]. We believe that adopting this algorithm for targeted intensified case finding could be crucial for improving early diagnosis and finding the missing cases that the National Tuberculosis Programme has been unable to reach thus far. In fact, the current double D strategy would have missed almost half of all TB cases in our study, comparable to the estimated 42% of undiagnosed TB cases in Vietnam in 2020 [3]. This does not account for an additional consideration: the current double D strategy is not done all at once, unlike the strategies in our analysis. As such, it would likely suffer from a much higher dropout rate (27% in a previous study among PWID in this setting [7]), meaning that we possibly overestimated the yield of the strategy herein.

A 2021 review of TB screening costs and cost-effectiveness in high-risk groups analyzed a large number of studies surveying key populations, including PWID (1 from 2011). Almost every study included TB symptoms using the WHO-recommended 4 symptom screen as a first triage step [23]. The review was used to inform the current WHO guidelines of systematic screening for TB disease, in which symptoms are still the first triage for high-risk groups [12]. However, our results further confirm the notion that asymptomatic cases make up a large proportion of TB cases [13–15]. Although the current symptom-based strategy achieves the lowest cost per case identified, the 44% sensitivity and high number of missed cases (false negatives) are highly dissatisfactory, especially considering that it is likely overestimated. Our results corroborate a 2022 review evaluating TB symptoms and CXR screening for TB disease, which found that CXR alone, regardless of symptoms, would be highly suggestive of TB disease [36]. As such, intensified case finding should not limit testing to those with a positive symptom screen result to improve case detection among people with an otherwise low probability of being diagnosed, such as PWID.

The application of our screening algorithm and all the screening tests at the community level, based on an RDS recruitment approach, appear feasible and acceptable, with the notable involvement and support from CBOs and peer educators. CBOs provide a setting for screening that is safe, comfortable, and free of stigma for PWID; they provide TB information and raise awareness; and they participate in sample collection. The proposed strategy would not require on-site medical personnel during screening, other than a radiographer for CXR using a portable x-ray machine, and participants would not have multiple visits in health clinics to get tested and results but just a onetime screening.

The trade-off of the selected algorithm is that it does not boast the highest PPV, with almost 1 in 2 referrals not being

a true TB case, and should therefore not be used as a diagnostic tool but rather a guide for referral. Further case-by-case investigation by medical personnel is necessary for this screening algorithm for those without a positive result from Xpert on sputum to review potentially non-TB abnormalities or TB sequelae [37]. Indeed, most of the wrongly referred participants had a history of TB, for which current CAD4TB algorithms are unable to differentiate from current TB disease, explaining the elevated rate of false positives with this tool among PWID. However, these cases of highly abnormal CXR readings could likely lead to lung function assessment or the diagnosis of other underlying conditions and ultimately benefit the patients. The number of missed cases herein is consistent with the sensitivity of Xpert MTB/RIF on sputum and thus the expected false negatives when screening large numbers of participants. Four participants classified as having confirmed TB had normal CXR findings, no symptoms, normal CRP values, and no known TB contacts and yet tested positive on Xpert on sputum. These participants may require a second positive Xpert test result (or smear or culture) before initiating treatment. Of note, initial exploratory analyses showed that the CRP levels in participants were not a discriminant tool for TB in this specific population, likely due to other sources of inflammation among many participants, further highlighting the need to design and select screening strategies with the target population in mind.

There are several limitations to our study. The first is that the cost per case detected, incremental cost-effectiveness ratio, yield, and PPV reported herein are highly dependent on TB prevalence, and as such, our screening algorithm applies only to high-risk populations. Populations with lower prevalence of TB disease will likely see lower PPV and higher costs per case detected if this strategy is applied. Second, we did not have a threshold for defining acceptability or willingness to pay in terms of cost per case detected as, to our knowledge, there are no other such community-based, PWID-specific screening strategies in Vietnam. Moreover, costs are considered from only the provider perspective and do not account for any patient costs related to screening, diagnosis, or treatment or for the potential effect of referring people without TB to health care structures—which could lead to diminished trust or health care fatigue, although non-TB abnormalities and impaired lung function may be detected. The focus on case detection also does not account for the many clinical challenges surrounding treatment initiation or adherence, which is required for diminished transmission and reduced incidence of TB cases, especially among asymptomatic cases (ie, patients who may not perceive themselves to have an illness necessitating treatment). The impact of this screening algorithm on onward transmission in this high-risk population is the aim of the larger, ongoing DRIVE-TB study.

CONCLUSION

Our results suggest that the following could improve the efficiency of TB screening strategies among PWID for a reasonable cost per patient: using computer-aided mobile CXR, followed by Xpert on sputum for those with a TB likelihood ≥50, referral to treatment for all persons with Xpert positive results, and further diagnostic confirmation for those with a TB likelihood ≥70 on CXR. This strategy could be an important step in closing the gap between theoretical guidelines and their real-life implementation, given available resources. It also makes the case that active case finding and systematic screening strategies should not limit testing to those with a positive symptom screen result, to maximize case finding and provide more accurate estimates of TB prevalence.

Supplementary Data

Supplementary materials are available at *Open Forum 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

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Data availability. The data that support the findings of this study are available from the corresponding author upon reasonable request.

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