Clinical evaluation of computer-aided digital x-ray detection of pulmonary tuberculosis during community-based screening or active case-finding: a case–control study

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Summary

Background Computer-aided detection (CAD) has been recommended as a tuberculosis screening tool. However, there are limited data about its utility, specifically in a community-based setting where the targeted population and the highest burden of undetected individuals resides. The aim of this study was to evaluate the diagnostic accuracy and clinical utility of CAD during community-based active case-finding (ACF) for tuberculosis.

Methods In this case–control study, we used individual patient data from adults aged 15 years or older who resided in tuberculosis-endemic or HIV-endemic communities, pooled from five community-based ACF studies in South Africa from November, 2016 to August, 2023. Cases were defined as participants who were tuberculosis positive (diagnosed with pulmonary tuberculosis by sputum Xpert Ultra or culture positivity, or both) and controls were tuberculosis negative. Controls were randomly sampled from each study at an approximate 1:2 ratio (case to control). We assessed CAD-interpreted chest radiography (CAD4TB version 7) against a microbiological reference standard. Diagnostic accuracy of CAD was determined by sensitivity, specificity, and area under the receiver operating curve (AUC). CAD performance was additionally assessed in various subgroups. We evaluated the clinical utility of CAD and performed a preliminary cost analysis comparing the cost per tuberculosis case detected and initiated on treatment (per 10 000 individuals screened) for two community-based diagnostic strategies: Xpert Ultra in everyone screened versus Xpert Ultra only in CAD-positive individuals.

Findings Of the 20 770 individuals enrolled across all studies, 530 (2·6%) had microbiologically proven tuberculosis. Data were available for 501 (94·5%) of the individuals with tuberculosis (cases) and 938 tuberculosis-negative individuals (controls). CAD achieved an AUC of 0·83 (95% CI 0·80–0·85). At a fixed sensitivity of 90% (threshold: 5) specificity was 44·9% (95% CI 42·5–47·3) and at a fixed sensitivity of 85% (threshold: 10) specificity was 54·1% (51·7–56·5). In the subgroup analysis, CAD performed worse in people living with HIV compared with HIV-negative people (AUC of 0·76 [0·71–0·81] *vs* 0·85 [0·82–0·87]; p=0·0037) and in asymptomatic people compared with symptomatic people (0·79 [0·76–0·82] *vs* 0·85 [0·82–0·88]; p=0·0079. Nevertheless, a CAD-directed Xpert Ultra strategy reduced costs by 20–53% compared with a universal Xpert Ultra only strategy (US$2207–$3745 *vs* $4698 per tuberculosis case detected and initiated on treatment per 10 000 people screened), at the detriment of lower diagnostic yield (40–59% *vs* 65% per 10 000 individuals screened).

Interpretation In the setting of community-based ACF, CAD did not meet the WHO screening test target product profile (>90% sensitivity and >70% specificity) and performed more poorly in some subgroups. However, a context-specific CAD-directed strategy could still be cost saving. These data inform community-based ACF strategies aiming to disrupt the tuberculosis transmission cycle.

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Introduction

Of the 10·8 million people who were estimated to have fallen ill with tuberculosis in 2023, approximately 2·7 million (one in three) were undiagnosed or unreported.[1] These missing millions are a potential source of transmission in their households and communities. Moreover, it is estimated that more than half of individuals with microbiologically confirmed tuberculosis are asymptomatic (ie, subclinical) and yet probably sentinels for disease transmission.[2] Therefore, early detection of tuberculosis through community-based active case-finding (ACF) might improve access to care and circumvent considerable transmission compared to symptomatic patients self-reporting to health-care facilities (passive case-finding).[3,4] However, community-based detection requires sensitive, user-friendly, and economically feasible screening and triage tools.

Research in context

Evidence before this study

Since the 2021 endorsement by WHO for the use of computer-aided detection (CAD) for screening and triage to detect tuberculosis there has been great interest in its clinical utility. However, there are hardly any data about CAD performance in the very population that the test is supposed to target—ie, individuals residing in high prevalence communities where CAD will be used as a community-based screening test. Indeed, most available data pertain to patients self-reporting to clinics where the profile and disease burden is different (more advanced). Furthermore, there are limited CAD data from HIV-endemic settings. We searched PubMed from database inception to May 1, 2024, to identify articles in any language that evaluated the performance of CAD during community-based screening or active case-finding (ACF) for tuberculosis. A search with no restrictions using the search terms ("tuberculosis" OR "TB") AND ("computer aided detection" OR "computer assisted diagnosis" OR "artificial intelligence") AND ("active case finding" OR "systematic screening") yielded 299 citations. Most reports either (1) recruited participants predominantly during passive case-finding (PCF: patients self-reporting to health-care facilities), including two systematic reviews, (2) focused on technical aspects of artificial intelligence, or (3) explored how CAD impacted tuberculosis services. 13 articles reported on CAD diagnostic accuracy during ACF for tuberculosis (including four studies which recruited participants during both ACF and PCF), but study sample size was small, and they used various (and older) CAD versions, thresholds, and differing reference standards (eg, human reader and Xpert Ultra alone). Four articles reported on cost-effectiveness highlighting the cost-saving potential of CAD. However, there are no large studies that evaluated CAD performance exclusively during community-based ACF for tuberculosis and furthermore in an HIV-endemic setting.

Added value of this study

To our knowledge, this is the first and largest comprehensive study that has evaluated CAD performance exclusively during community-based ACF for tuberculosis in an HIV-endemic setting. Furthermore, we report CAD accuracy against a robust microbiological reference standard (ie, Xpert MTB/RIF Ultra and sputum culture) unlike many previous studies and have used the latest available CAD version (CAD4TB version 7). This study yielded important insights for tuberculosis ACF programmes, including evaluating the optimum CAD threshold to be used in an endemic setting (which is controversial), and performance in various subgroups (eg, people living with HIV, asymptomatic individuals, and people with a history of tuberculosis). We have shown that with a high sensitivity, CAD could have a major impact on diagnostic yield compared with standard approaches. Furthermore, despite its modest specificity of approximately 50% (and not meeting WHO target profiles), CAD could still be cost saving without missing too many individuals with tuberculosis and reduce the total number of false positive Xpert Ultra results (because fewer are tested using the CAD-directed strategy). The cost-saving aspect is crucial in the context of rolling out large-scale community-based ACF strategies. Finally, we also showed for the first time that CAD detected almost all individuals with probably infectious tuberculosis, a crucial finding in the context of global efforts to interrupt community-based tuberculosis transmission.

Implications of all the available evidence

Despite not meeting the WHO target product profile for tuberculosis, and the modest specificity, our study suggests that in the context of community-based screening or ACF, CAD has the potential to be a useful and cost-saving screening tool for tuberculosis in HIV-endemic and resource-poor settings. Furthermore, by detecting most people with probably infectious tuberculosis, CAD can probably interrupt the tuberculosis transmission cycle. Our findings inform policy makers and national tuberculosis programmes about how CAD can be implemented in specific contexts.

Chest radiography is one of the most sensitive tests for detecting active tuberculosis.[5] Although there have been advances in digital radiography technology, limitations still exist including restricted access in low-resource settings, inter-reader and intra-reader variability, and low specificity, especially in endemic areas where the prevalence of HIV and history of previous tuberculosis is high.[6] However, the rise of artificial intelligence-based computer-aided detection (CAD) has afforded a potential opportunity to streamline screening strategies through early detection of tuberculosis-related radiological abnormalities. CAD makes use of deep neural networks and identifies abnormalities on radiological images suggestive of tuberculosis. Results are expressed as abnormality scores (either 0–100 or 0–1) that are dichotomised (tuberculosis likely or not) at a chosen threshold. If above the threshold, images are considered positive or abnormal, and the individual is deemed at greater risk for tuberculosis and should undergo confirmatory microbiological testing (nucleic acid amplification test or sputum culture, or both). Crucially, threshold determination requires careful consideration and remains unclarified for community-based individuals who generally have a lower burden of disease.

Studies have reported CAD to be a sensitive tool with similar or better accuracy compared with expert human chest x-ray readers.[7,8] In 2021, WHO endorsed the use of chest radiography and CAD for pulmonary tuberculosis screening.[9] However, the recommendation was conditional (not mandatory for programmes) with very low certainty of evidence, and most published literature was obtained in the context of passive case-finding (where disease burden is more severe, score thresholds

higher, and where findings might not apply to community-based cohorts). Thus, there are hardly any data about CAD performance in the very population that the test is supposed to target—ie, individuals residing in high prevalence communities where CAD will be used as a community-based screening or triage test. There are also limited data about the clinical implications of CAD accuracy estimates with newer CAD versions, cost implications, performance in HIV-endemic settings, and whether it can detect probably infectious individuals thus interrupting community-based transmission. To address these knowledge gaps, we evaluated the diagnostic accuracy and clinical utility of CAD during community-based ACF for pulmonary tuberculosis in HIV-endemic communities using a robust reference standard (often lacking in published studies).

Methods

Study design and participants

In this case–control study, we pooled and analysed individual patient data from five multicentre, community-based ACF for tuberculosis studies conducted in South Africa. The data in these five studies were collected from November, 2016 to August, 2023. The methods for each study have been described previously.[10–14] Briefly, individuals aged 15 years or older who resided in tuberculosis-endemic or HIV-endemic communities were included. All participants underwent an initial WHO tuberculosis symptom screen (including cough, fever, night sweats, and weight loss). Participants from two studies[10,11] underwent diagnostic sputum sampling if they reported any WHO tuberculosis symptom or their screening chest x-ray was deemed abnormal by human readers or CAD, with or without symptoms. The remaining three studies[12–14] performed diagnostic sputum testing on all eligible participants who reported any WHO tuberculosis symptom or had high-risk factors for tuberculosis (ie, people living with HIV, contacts, a history of previous tuberculosis, or diabetes), and whether symptoms were present or not. Three studies[10,11,14] performed chest x-rays on all eligible participants, and two studies[12,13] only performed chest x-rays on individuals who were either HIV positive, household contacts, or diagnosed with tuberculosis. Thus, the studies included both asymptomatic and symptomatic people.

All included studies received ethical approval, and all participants provided informed consent. The current study was ethically approved by the University of Cape Town Human Research Ethics Committee (UCT HREC 005/2023). This report follows the STARD guidelines for diagnostic accuracy evaluations[15] and STROBE guidelines for reporting observational studies (appendix pp 3–4).[16]

Procedures

Demographic, clinical, and microbiological data were obtained from each study. The GeneXpert MTB/RIF Ultra (Xpert Ultra, Cepheid, Sunnyvale, CA, USA) nucleic acid amplification test was used in all studies. Similarly, for tuberculosis sputum culture, all five studies used liquid culture (Bactec MGIT 960, Becton Dickinson, Franklin Lakes, NJ, USA). In three studies,[12–14] tuberculosis-positive individuals underwent microbiological infectiousness studies, including sputum smear microscopy with Ziehl–Neelsen staining and cough aerosol sampling studies (CASS; a validated system that measures culturable *Mycobacterium tuberculosis* in cough aerosol droplets <10 µm in diameter[17]).

Chest x-ray images were anonymised and collected in DICOM format from three studies,[12–14] with CAD analysis subsequently performed using CAD4TB version 7 software (Delft Imaging, Hertogenbosch, Netherlands). For the remaining two studies,[10,11] investigators of the studies (overseen by TM, ZZQ, MvdW, JF, ADG, and EBW) provided CAD scores generated by the same software and version. All CAD analyses were performed independently and no images in the current study were used for CAD training. The CAD developers had no access to the images and were not involved in the conceptualisation or analysis of this study. Chest x-rays were additionally reviewed by expert human readers in the original studies (including PG) to detect lung abnormalities, including cavitary disease as a marker for active disease and probable infectiousness.

In our study, cases were defined as participants who were tuberculosis positive—ie, individuals diagnosed with pulmonary tuberculosis by Xpert Ultra or sputum culture positivity, or both (microbiological reference standard). We defined controls as participants who were tuberculosis negative—ie, individuals with both a negative Xpert Ultra and sputum culture result. For controls, we randomly sampled from tuberculosis-negative individuals in each study and used an approximate 1:2 ratio of cases to controls. Random sampling was performed by an independent investigator using STATA. We additionally evaluated CAD against other reference standards: Xpert Ultra (trace only excluded) or sputum culture positivity (or both), Xpert Ultra positivity only, and sputum culture positivity only.

Statistical analysis

At 90% sensitivity and 70% specificity, as per the WHO target product profile (TPP) for a screening or triage test,[18] and assuming a precision level of plus or minus 5%, the minimum required sample size was 276 (138 tuberculosis cases and 138 non-tuberculosis controls: WHO CAD calibration toolkit[19]).

Categorical variables were compared using χ^2 test or Fisher's exact test. Continuous variables were compared using Student's *t* test (parametric data) or the Mann–Whitney test (non-parametric data). Diagnostic accuracy was determined by sensitivity, specificity, and area under the receiver operating curve (AUC) of the index test (ie, CAD) and expert human reader against the

See Online for appendix

microbiological reference standard. We analysed the performance of CAD against the WHO TPP by first calculating the sensitivity and specificity of CAD across all thresholds (0–100). Subsequently, we identified the threshold that resulted in a sensitivity closest to 90% and reported the corresponding specificity. The same analysis was then performed in reverse to evaluate the sensitivity achieved when specificity was closest to 70%. We also evaluated CAD performance at additional fixed sensitivities and specificities, and at the developer-calibrated threshold (50: CAD4TB version 7). CAD performance was additionally evaluated in various subgroups: age, sex assigned at birth, HIV status, diabetes status, history of previous tuberculosis, and presence of symptoms. In each subgroup, the AUC was calculated and compared. Furthermore, optimal thresholds for achieving desired sensitivity and specificity in each subgroup were evaluated. Multivariable analyses were conducted to investigate the impact of demographic and clinical variables on CAD performance (appendix pp 14–15).

In a subanalysis using data from three studies,[12–14] we investigated the accuracy of CAD to identify patients with probably infectious tuberculosis at various thresholds. We used a composite measure previously described:[12] smear positivity, CASS positivity, or cavitary disease detected on chest x-ray by the expert human reader (only in patients with newly diagnosed tuberculosis to limit potential bias of cavities from previous tuberculosis).

To determine the potential clinical use of CAD programmatically, we determined the number of tuberculosis-positive individuals missed (ie, CAD false negatives), the number of confirmatory diagnostic tests saved or not required (ie, CAD true negatives), and the number of falsely required confirmatory diagnostic tests (ie, CAD false positives) in a hypothetical population of 10 000 individuals screened at various accuracy estimates and tuberculosis prevalences.

We conducted a preliminary economic analysis comparing the cost per tuberculosis case detected and initiated on treatment (per 10 000 individuals screened) for two community-based tuberculosis diagnostic strategies: Xpert Ultra in everyone screened (Xpert only) versus Xpert Ultra only in CAD-positive individuals (CAD–Xpert). Test costs were calculated using a bottom-up ingredient's approach where each individual test cost was calculated by combining each component cost of the test (labour, equipment, and consumables), and then multiplied by the calculated number of tests performed for each strategy. Tuberculosis treatment costs were obtained from published sources.[1] Costs were expressed in 2024 US$ at the exchange rate of ZAR 19·22 to $1.[20] Tuberculosis prevalence[10] and test performance estimates from published[12,21] and ongoing[13,14] studies were used to calculate test outcome probabilities. Outcomes included the number of Xpert Ultra tests performed, number of tuberculosis cases detected, and the diagnostic yield among all people tested and diagnosed.[22] We performed a univariate analysis to assess the impact of uncertainties around input parameters. Additional methodological details of the preliminary cost analysis are in the appendix (pp 20–24).

Analyses were performed using SPSS Statistics (version 28.0), GraphPad Prism (version 10.2.3; GraphPad Software Boston, MA, USA), and R (version 4.2.3).

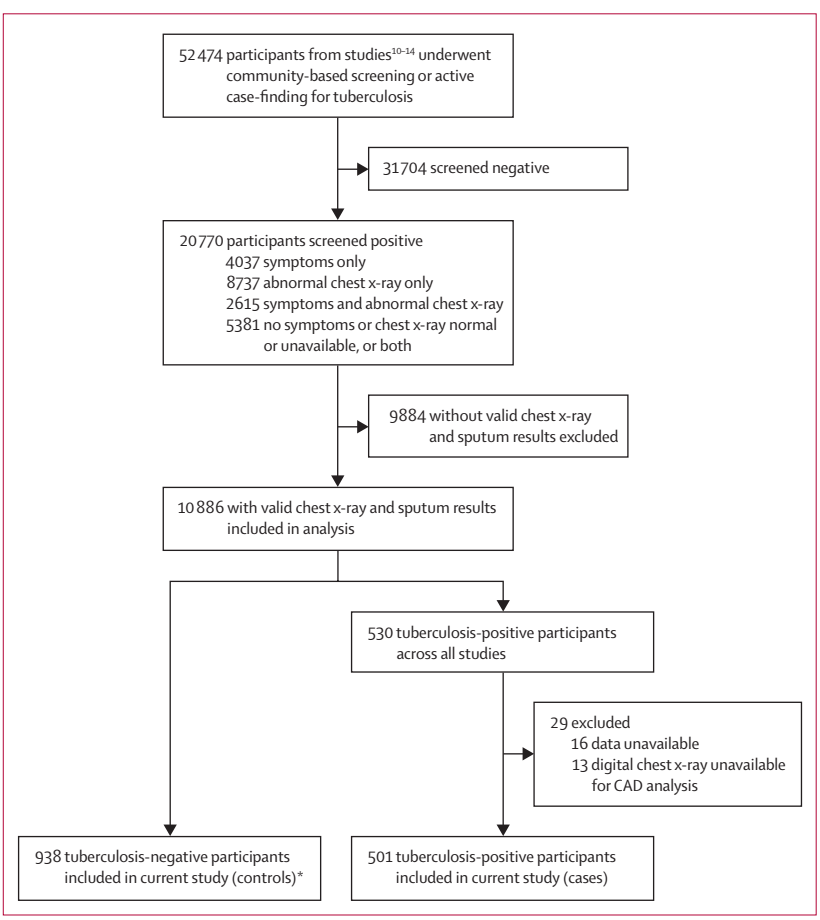

Figure 1: **Study overview**
CAD=computer-aided detection. *Controls randomly sampled from tuberculosis-negative individuals in each study in an approximate 1:2 ratio (case to controls).

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

Results
Across all five community-based ACF studies, 52 474 individuals were screened, of which 20 770 (39·6%) screened positive for either the presence of WHO tuberculosis-related symptoms or high-risk factors for tuberculosis, or an abnormal screening chest x-ray (figure 1). 530 (2·6%) individuals were diagnosed with tuberculosis. Data from 29 tuberculosis-positive

	Overall (n=1439)	Tuberculosis positive (n=501)	Tuberculosis negative (n=938)	p value
Age, years	45 (32–59)	43 (31–54)	47 (32–61)	0·0009
≤55	983 (68·3%)	385 (76·8%)	598 (63·8%)	<0·0001
>55	456 (31·7%)	116 (23·2%)	340 (36·2%)	..
Sex at birth				
Female	751 (52·2%)	238 (47·5%)	513 (54·7%)	0·0093
Male	688 (47·8%)	263 (52·5%)	425 (45·3%)	..
Current smoker*	570/1139 (50·0%)	223/402 (55·5%)	347/737 (47·1%)	0·0068
Alcohol user	520 (36·1%)	178 (35·5%)	342 (36·5%)	0·53
HIV positive	354 (24·6%)	141 (28·1%)	213 (22·7%)	0·023
Diabetes†	66/994 (6·6%)	15/354 (4·2%)	51/640 (8·0%)	0·024
History of previous tuberculosis	421 (29·3%)	193 (38·5%)	228 (24·3%)	<0·0001
Presence of symptoms	..	..	..	0·0006
Asymptomatic	730 (50·7%)	285 (56·9%)	445 (47·4%)	..
Symptomatic	709 (49·3%)	216 (43·1%)	493 (52·6%)	..
Cough	517 (35·9%)	170 (33·9%)	347 (37·0%)	0·25
Cough >2 weeks	266 (18·5%)	82 (16·4%)	184 (19·6%)	0·13
Fever	184 (12·8%)	58 (11·6%)	126 (13·4%)	0·32
Night sweats	373 (25·9%)	127 (25·3%)	246 (26·2%)	0·72
Unintended weight loss	308 (21·4%)	113 (22·6%)	195 (20·8%)	0·44
Xpert or culture positive, or both	501 (34·8%)	501 (100%)	..	..
Xpert or culture positive or both (trace only excluded)	461 (32·0%)	461 (92·0%)	..	..
Xpert positive only	158 (11·1%)	158 (31·5%)	..	..
Culture positive only	96 (6·7%)	96 (19·2%)	..	..
Xpert and culture positive	247 (17·2%)	247 (49·3%)	..	..
CAD4TB version 7 score	17·8 (3·0–59·1)	67·9 (26·2–87·7)	6·6 (1·4–27·4)	<0·0001
Any chest x-ray abnormality as assessed by expert human reader	900 (62·5%)	429 (85·6%)	471 (32·7%)	<0·0001
Chest x-ray features consistent with active tuberculosis as assessed by expert human reader	696 (48·4%)	354 (70·7%)	342 (36·5%)	<0·0001

Data are median (IQR), n (%) or n/N (%). CAD=computer-aided detection. Xpert=GeneXpert MTB/RIF Ultra. *Not reported in 300 participants. †Not reported in 445 participants.

Table 1: **Demographic, clinical, microbiological, and radiological characteristics of study participants (n=1439)**

	Threshold score	True positive	False positive	True negative	False negative	Sensitivity (95% CI)	Specificity (95% CI)
Sensitivity							
Sensitivity fixed at 90%	5	453	517	421	48	90·4% (88·1–92·7)	44·9% (42·5–47·3)
Sensitivity fixed at 85%	10	428	431	507	73	85·4% (83·0–87·8)	54·1% (51·7–56·5)
Sensitivity fixed at 80%	17	402	332	606	99	80·2% (77·9–82·6)	64·6% (62·3–66·9)
Specificity							
Specificity fixed at 70%	24	382	276	662	119	76·2% (73·9–78·6)	70·6% (68·2–73·0)
Specificity fixed at 65%	18	396	320	618	105	79·0% (76·6–81·4)	65·9% (63·5–68·3)
Developer-calibrated threshold*	50	311	97	841	190	62·1% (59·7–64·5)	89·7% (87·3–92·1)
Expert human reader							
Any chest x-ray abnormality	..	429	471	467	72	85·6% (82·3–88·6)	49·8% (46·5–53·0)
Chest x-ray features consistent with active tuberculosis	..	354	342	596	147	70·7% (66·5–74·6)	63·5% (60·4–66·6)

*CAD4TB version 7.

Table 2: **Computer-aided detection and expert human reader accuracy estimates (n=1439)**

individuals were unavailable. Therefore, 1439 individuals were included for analysis in the current study (501 tuberculosis positive [cases] and 938 tuberculosis negative [controls]; appendix p 5).

Tuberculosis-positive individuals were significantly younger (43 years [IQR 31–54] *vs* 47 years [32–61]; p=0·0009) and predominantly male (263 [52·5%] of 501 *vs* 425 [45·3%] of 938; p=0·0093) compared with

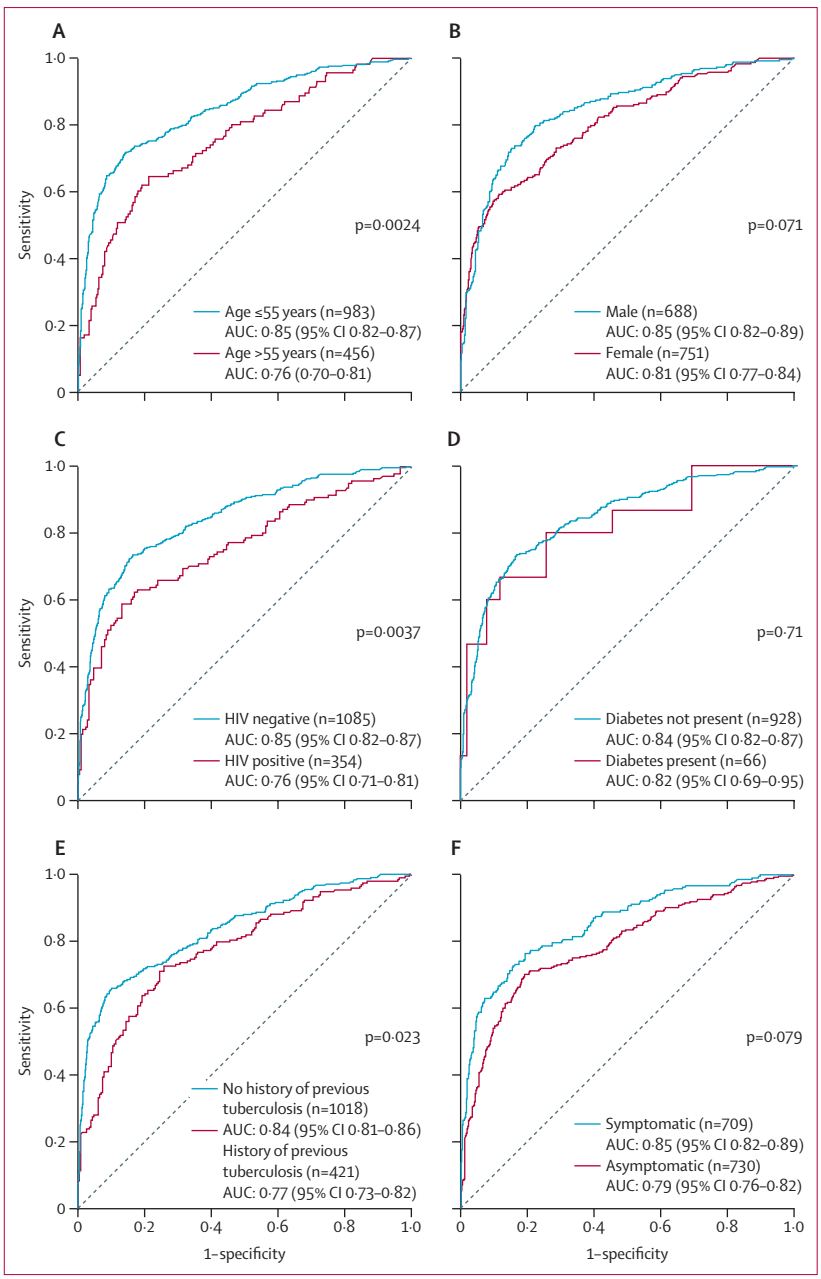

Figure 2: **AUC subgroup analysis of computer-aided detection against the microbiological reference standard (n=1439).**
Subgroups include age (A), sex (B), HIV status (C), diabetes status (D), tuberculosis history (E), and presence of symptoms (F). AUC=area under the receiver operating curve.

tuberculosis-negative individuals (table 1). 354 (24·6%) participants were HIV positive and 421 (29·3%) had a history of previous tuberculosis. A significantly higher proportion of tuberculosis-positive individuals were asymptomatic at enrolment compared with tuberculosis-negative individuals (285 [56·9%] of 501 *vs* 445 [47·4%] of 938; p=0·0006). Among the 501 tuberculosis-positive individuals, 158 (31·5%) were Xpert Ultra positive only, whereas 96 (19·2%) were sputum culture positive only, and 247 (49·3%) were both Xpert Ultra and sputum culture positive. The median CAD4TB version 7 score for the total cohort was 17·8 (IQR 3·0–59·1), with significantly higher scores in tuberculosis-positive individuals compared with tuberculosis-negative individuals (67·9 [26·2–87·7] *vs* 6·6 [1·4–27·4]; p<0·0001). A summary of demographic, clinical, microbiological, and radiological characteristics within each study is in the appendix (p 6).

CAD achieved an AUC of 0·83 (95% CI 0·80–0·85). No significant differences were found in AUC between various microbiological reference standards (appendix p 7) or between studies (appendix p 8). CAD specificity was 44·9% (95% CI 42·5–47·3) at a fixed sensitivity of 90% (threshold 5), 54·1% (51·7–56·5) at a fixed sensitivity of 85% (threshold 10), and 64·6% (62·3–66·9) at a fixed sensitivity of 80% (threshold 17; table 2). Conversely, the CAD sensitivity was 76·2% (73·9–78·6) at a fixed specificity of 70% (threshold 24) and 79·0% (76·6–81·4) at a fixed specificity of 65% (threshold 18). At the developer-calibrated threshold (50: CAD4TB version 7), CAD sensitivity was 62·1% (59·7–64·5) and specificity was 89·7% (87·3–92·1). CAD accuracy was similar when Xpert Ultra trace only results were excluded (appendix p 9). Compared with the expert human reader detecting chest x-ray features consistent with active tuberculosis, CAD had improved specificity at the same sensitivity of approximately 85% (54·1% [51·7–56·5] *vs* 49·8% [46·5-53·0]). The accuracy estimates of CAD and expert human reader stratified by study are in the appendix (p 10).

There were significant differences in AUC between subgroups with CAD performing worse in individuals older than 55 years compared with individuals aged 55 years or younger (0·76 [95% CI 0·70–0·81] *vs* 0·85 [0·82–0·87]; p=0·0024), HIV-positive compared with HIV-negative people (0·76 [0·71–0·81] *vs* 0·85 [0·82–0·87]; p=0·0037), individuals with a history of previous tuberculosis compared with those without (0·77 [0·73–0·82] *vs* 0·84 [0·81–0·86]; p=0·023), and asymptomatic people compared with people with symptoms (0·79 [0·76–0·82] *vs* 0·85 [0·82–0·88]; p=0·0079; figure 2). Similar differences in CAD sensitivity and specificity were found in the same subgroups (appendix pp 11–12). Furthermore, thresholds varied considerably between subgroups and required adjustment to achieve either 90% sensitivity or 70% specificity. Sensitivity and specificity of the expert human reader between subgroups are in the appendix (p 13). Results of the multivariable analyses are in the appendix (pp 16–17).

374 participants from three studies[12–14] were included in a subanalysis evaluating CAD performance in detecting probably infectious tuberculosis (ie, smear positive, CASS positive, cavitary disease on chest x-ray in patients with newly diagnosed tuberculosis, or a combination of all three; figure 3). Of participants that were tuberculosis

positive and underwent all infectiousness testing (131 [35·0%] of 374), 44 (33·6%) were probably infectious. CAD achieved an AUC of 0·87 (95% CI 0·81–0·93) in detecting probably infectious tuberculosis. At a threshold of 5 CAD sensitivity was 100·0% (95% CI 92·0–100·0), at a threshold of 10 CAD sensitivity was 93·2% (81·8–97·7), and at a threshold of 17 CAD sensitivity was 93·2% (81·8–97·7).

The potential clinical implications of CAD accuracy estimate per 10 000 individuals screened at various tuberculosis prevalences are in the appendix (pp 18–19). For example, at a 1% tuberculosis prevalence, and a CAD sensitivity of 90·4% and specificity of 44·9% (threshold: 5), CAD would miss ten tuberculosis positives (ie, false negatives) and would be falsely positive (and therefore falsely require confirmatory diagnostic testing) in 5455 (54·5%) of 10 000 people screened. However, 4445 (44·5%) 10 000 individuals would be truly CAD negative (therefore truly not requiring a confirmatory diagnostic test and saving cost during screening strategies).

A CAD–Xpert strategy was more economical compared with an Xpert only strategy (US$2207–$3745 *vs* $4698 per tuberculosis case detected and initiated on treatment per 10 000 people screened) with savings between $953 and $2940 depending on the CAD threshold used (table 3). At a lower CAD threshold (threshold: 5), the Xpert only strategy had a higher diagnostic yield compared with the CAD–Xpert strategy (65% *vs* 59% per 10 000 individuals screened). However, the CAD–Xpert strategy still had a lower cost per tuberculosis case detected and initiated on treatment due to lower overall costs associated with false positives (ie, less Xpert Ultra tests performed) and fewer people being initiated on treatment. At higher CAD thresholds (24 and 50), which favour higher test specificities at the expense of sensitivity, strategy costs were even lower (due to fewer false positives) but showed up to 25% lower diagnostic yield compared to the Xpert only strategy (table 3). Nevertheless, using higher CAD thresholds yielded the lowest cost per tuberculosis case detected and initiated on treatment for the CAD–Xpert strategy. Univariate sensitivity analyses revealed that, for both Xpert only and CAD–Xpert strategies (using a CAD threshold of 5), Xpert Ultra specificity, sensitivity, and tuberculosis prevalence were the most influential parameters on the cost per case detected and initiated on treatment (appendix p 25). However, even at different estimates for these parameters, the CAD–Xpert strategy, especially at higher thresholds, always had lower cost per tuberculosis case detected and initiated on treatment compared to the Xpert only strategy (appendix p 26).

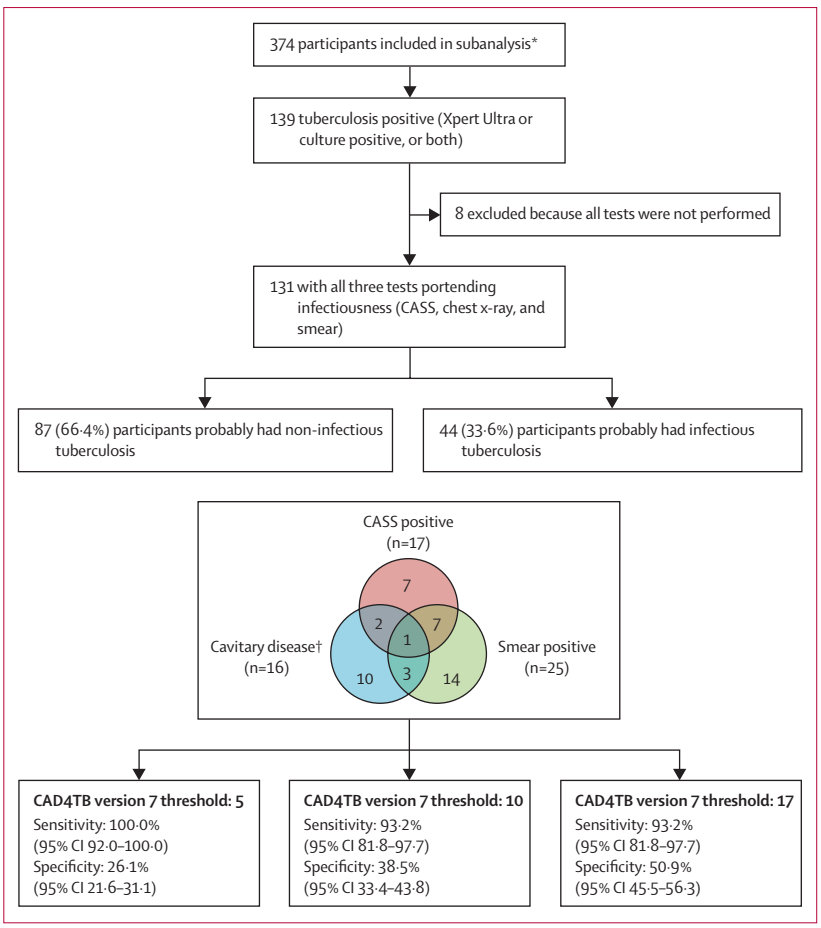

Figure 3: **Subanalysis: accuracy of CAD to detect probably infectious patients with tuberculosis at various thresholds (n=374)**
CAD=computer-aided detection. CASS=cough aerosol sampling studies. Xpert=GeneXpert MTB/RIF Ultra. *Only data from the XACT-2,[12] XACT-3,[13] and XACT-19[14] studies were included. †Cavitary disease detected on chest x-ray by expert human readers in patients with newly diagnosed tuberculosis.

Discussion

To our knowledge, this is the largest study evaluating the diagnostic accuracy and clinical utility of CAD during community-based ACF for tuberculosis. Our study suggests that in the context of community-based screening or ACF, and despite not meeting the WHO TPP, CAD has the potential to be a useful and cost-saving screening tool for tuberculosis in an HIV-endemic and resource-poor setting. Furthermore, by detecting most people with probably infectious tuberculosis, CAD could assist in interrupting the tuberculosis transmission cycle. Our findings inform policy makers and national tuberculosis programmes about how CAD can be implemented in specific contexts.

Against a microbiological reference standard, we found CAD to have good accuracy (AUC>0·80) which is complemented by findings of other ACF studies.[23–27] However, CAD had modest specificity which might be attributed to uncertainty of chest x-ray features of active tuberculosis, especially in settings with high prevalences of HIV, asymptomatic tuberculosis, and history of previous tuberculosis. A 2024 study[28] estimated CAD accuracy during ACF for tuberculosis using six methodological approaches, including a latent class analysis. The authors suggested that not including

	Xpert only (Xpert in all people screened)	CAD–Xpert (Xpert only in CAD-positive individuals)		
		CAD4TB version 7 threshold: 5 (sensitivity ≥90%)	CAD4TB version 7 threshold: 24 (specificity ≥70%)	CAD4TB version 7 developer-calibrated threshold: 50
Costs*				
Total cost of each strategy	$305 338	$220 036	$145 636	$89 086
Total test costs	$168 920	$132 968	$89 750	$57 571
Total treatment costs	$136 418	$87 068	$55 886	$31 516
Costs incurred due to false positive results	$106 047	$58 861	$31 407	$11 003
Costs incurred due to false negative results	$591	$697	$649	$601
Outcomes				
Number of Xpert tests performed	10 000	5545	2987	1082
Total people with tuberculosis (assuming 1% tuberculosis prevalence)	100	100	100	100
Number of tuberculosis cases detected (true positive)	65	59	50	40
Number of tuberculosis cases missed (false negative)	35	41	50	60
Number of cases incorrectly diagnosed (false positive)	198	109	58	20
Diagnostic yield among all tested†	0·65% (65/10 000)	0·59% (59/10 000)	0·50% (50/10 000)	0·40% (40/10 000)
Diagnostic yield among all diagnosed‡	65·0% (65/100)	59·0% (59/100)	50·0% (50/100)	40·0% (40/100)
Cost per tuberculosis case detected and initiated on treatment*	$4698	$3745	$2940	$2207
Difference (% savings) compared to Xpert only strategy	..	$953 (20%)	$1757 (37%)	$2490 (53%)

Each measure is per 10 000 people screened at a tuberculosis prevalence of 1%. CAD=computer-aided detection. Xpert=GeneXpert MTB/RIF Ultra. *Costs are expressed in 2024 US$. †The number of people with a positive diagnosis by the test divided by the total number of people for whom tuberculosis testing was attempted. ‡The number of people with a positive diagnosis by the test divided by the total number of people diagnosed with tuberculosis.[22]

Table 3: **Costs, outcomes, and cost per tuberculosis case detected and initiated on treatment of each diagnostic strategy evaluated in the preliminary economic analysis**

individuals with normal appearing chest x-rays or who were asymptomatic severely underestimates specificity. Therefore, by assuming participants who were not microbiologically tested were tuberculosis negative, CAD accuracy might be better characterised, but risks missing individuals with asymptomatic (ie, subclinical) tuberculosis.

Threshold determination is crucial when implementing CAD. A high threshold might miss people with tuberculosis, whereas a low threshold will detect most individuals with tuberculosis but with greater costs due to increased confirmatory microbiological testing. Few studies have reported on optimal thresholds as they are population-specific and context-specific. The current study found a CAD4TB version 7 threshold of 5 had a sensitivity of 90% or more (compared with the developer-calibrated threshold of 50). We therefore provide important data on CAD threshold use in South Africa, and in a HIV-endemic setting where there is a high proportion of individuals with a history of previous tuberculosis. A previous community-based study in South Africa suggested a CAD4TB version 7 threshold of 20; however, this threshold was determined by comparing an assessment by a radiologist.[29] Contrastingly, a study using data collected during the Lesotho national prevalence survey reported a CAD4TB version 7 threshold of 9 achieving a minimum sensitivity of 90% with similar specificity to the current study.[28] Importantly, with the technological advances and refinements in algorithms and neural networks, implementers of CAD should ensure that threshold determinations are re-evaluated after newer CAD versions are released.

In a subgroup analysis, we found CAD performed significantly worse in individuals who were older, were HIV positive, had a history of previous tuberculosis, and in those who were asymptomatic. These results were consistent with previous studies.[7,8,23,27,30] The decreased performance by CAD in older individuals and people living with HIV is especially important as these subgroups have higher case fatality and therefore require greater urgency in initiating treatment. CAD performed worse in females compared with males; however, the difference was not significant. Our study found no difference in CAD accuracy in individuals with diabetes, contrary to findings in previous literature.[31] Thresholds

varied substantially between subgroups and highlight the importance of considering population characteristics when implementing CAD into ACF strategies. Studies have shown the potential improvement in CAD performance when combining demographic or clinical factors with continuous CAD scores through multivariable modelling.[27,32] Future research might look to improve and validate these predictive models through increased sample sizes, inclusion of more clinical variables, and utilising data from prospective, multicentre studies that may improve population-specific and context-specific generalisability.

A crucial goal of tuberculosis screening is to interrupt transmission by detecting infectious patients. Although there is no agreed upon definition of tuberculosis infectiousness, we used a previously established definition incorporating smear positivity, CASS positivity, or cavitary disease.[12] It is well established and accepted that smear positivity and cavitary disease are associated with tuberculosis infectiousness (and transmission),[33,34] with CASS being a measure of infectiousness that correlates with tuberculin skin test conversion and development of active tuberculosis within 2 years.[16,35] In our subanalysis, we showed that CAD has the potential to detect all probably infectious patients with tuberculosis. This finding has important public health implications because identifying probably infectious people allows for close follow-up and targeted interventions for these individuals, while also interrupting community-based transmission. Although CAD4TB only provides a CAD score and a binary classification of whether tuberculosis is likely present or not, other CAD software have the capability to report on lung abnormalities (eg, cavities) which has the potential to identify probably infectious individuals, which is an important basis for future work.

Limited data exist evaluating the clinical utility of CAD as a screening tool, including clinical implications of its accuracy estimates and economic feasibility. With CAD showing modest specificity, screening strategies are at risk for increased costs due to high numbers of people requiring confirmatory diagnostic testing. However, as a screening tool, it could be argued that the benefits of high sensitivity outweigh the limitations of a lower specificity. Indeed, the WHO TPP report noted the importance of considering the trade-off between cost and specificity, in addition to the potential burden on the health system when large numbers of patients who are false positive are tested.[18] Based on our findings, and at a 1% tuberculosis prevalence (like South Africa's national tuberculosis prevalence),[10] approximately half of all people screened would be falsely positive. However, approximately 45% would be truly negative and not require confirmatory testing, thereby saving overall costs. In our preliminary economic analysis, we found that a CAD-directed Xpert strategy (ie, performing Xpert Ultra only if CAD is positive) had a lower cost per case diagnosed and initiated on treatment when compared with performing Xpert Ultra in all people in an ACF setting, which is because less Xpert Ultra tests are performed, and overall false positive numbers are reduced. Our findings are corroborated by other studies,[36–38] and suggest that CAD could be a useful and cost-saving tool, especially during community-based ACF for tuberculosis in endemic settings. This approach could be combined with other cost-saving approaches such as sputum pooling strategies for Xpert testing.[39] However, the model did not account for the potential long-term benefits of early tuberculosis detection or the impact of missed tuberculosis cases, in terms of onward transmission and development of additional tuberculosis cases. These factors would need to be considered in future cost-effectiveness analyses using empirical data or more in-depth modelling, because it will probably affect the cost savings of these strategies. Other considerations (eg, settings, tuberculosis prevalence rates, combination of ACF screening tests, and choice of CAD threshold) also need to be addressed for optimal resource allocation.

Our study had several strengths. These included focusing on a community-based population where the test will be used, evaluation in HIV-endemic populations and other subgroups, inclusion of a preliminary cost analysis, and using a robust reference standard. However, there were also several limitations. We used a case–control design which might have introduced biased estimates of CAD diagnostic accuracy. Furthermore, studies with both observational and interventional study designs were included, which might have impacted results. However, study-specific populations were similar (ie, individuals who resided in tuberculosis-endemic or HIV-endemic communities at high risk for tuberculosis) and this was the largest community-based ACF for tuberculosis study that evaluated CAD performance against a microbiological reference standard. We only assessed one CAD product due to data availability and differences in individual study designs. However, we used the latest available CAD4TB version. We only included participants aged ≥15 years and could therefore not comment on the diagnostic accuracy of CAD in children and young adolescents, an important population that contributes approximately 5–10% of the global tuberculosis burden. However, WHO only recommends CAD as a screening or triage tool in individuals aged 15 years or older. Data were not collected evaluating participant or operator feedback and preferences on CAD. This important but often overlooked area of the research field should be the basis for future research. Not all participants underwent all infectiousness studies. Additionally, the composite measure for probably infectious tuberculosis included cavitary disease detected on chest x-ray, which might have preselected for a subset of infectious tuberculosis cases where CAD is likely to perform better (ie, x-ray identifiable disease). Nevertheless, this was a subanalysis, and the aim was to determine whether CAD

could not just detect microbiologically proven tuberculosis, but also detect probably infectious tuberculosis at the same threshold. Future larger studies are planned to corroborate our findings. Finally, we conducted a preliminary economic analysis showing the potential cost savings of CAD and could therefore not report on overall cost-effectiveness. However, prospective studies[13,14] performing comprehensive cost analyses are ongoing, which might verify our findings.

In conclusion, during community-based ACF for tuberculosis in an HIV-endemic setting, CAD did not meet the WHO TPP and performed more poorly in some subgroups. However, CAD might still be a useful screening tool that could detect not just people with microbiologically proven tuberculosis, but also people who are probably infectious. Furthermore, despite modest specificity and a high false positivity rate, a context-specific CAD-directed strategy could still be cost saving, especially during large-scale screening. Our findings inform community-based ACF strategies, national tuberculosis programmes, and global health bodies engaged in tuberculosis care and prevention, with the goal to disrupt the tuberculosis transmission cycle and end tuberculosis.

Contributors

AJS, TP, AP, AE, and KD conceptualised the study. AJS and TP accessed and verified the data. AJS, TP, AP, SO, SJ, JS, PG, TM, MvdW, ZZQ, JF, ADG, and EBW collected and curated the data. AJS, TP, AP, TM, MvdW, ZZQ, JF, ADG, and EBW did the methodology. AJS, TP, and AP did the formal analysis. KD, AE, MvdW, ADG, and EBW supervised the study. AJS wrote the original draft of the manuscript. All authors reviewed and critically revised the manuscript. All authors had full access to all data and agreed with the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

De-identified data from this study are available upon reasonable request to the corresponding author, provided investigators proposed use of the data has been approved by an independent ethical review committee.

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