Community-based tuberculosis screening with computer-aided detection technology alone and in combination with point-of-care C-reactive protein testing: a paired screen-positive trial

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Summary

Background Active tuberculosis case-finding in communities is crucial for early disease detection and disruption of transmission; however, it is complex and costly. A thorough analysis of tuberculosis screening strategies is essential, particularly because the health systems affected often have limited resources. We aimed to compare two community screening approaches in terms of tuberculosis case yield and cost.

Methods This pragmatic community trial, with a paired screen-positive design (ie, within-person comparison), was conducted in the Butha-Buthe District in Lesotho and the uMgungundlovu District in South Africa. All household members aged at least 18 years were eligible to participate, except those who were seriously ill, had a condition that prevented their safe and full participation, were receiving tuberculosis treatment, or were pregnant (Lesotho only). We compared two screening approaches: the use of computer-aided detection (CAD) software on digital chest x-rays alone (the CAD4TBv7 approach) and the use of CAD followed by a C-reactive protein (CRP) test if the CAD score was in a particular range (the CAD4TBv7-CRP approach). A confirmatory Xpert MTB/RIF Ultra test was conducted when required by the algorithm of one or both approaches. Coprimary outcomes were to establish whether the CAD4TBv7-CRP approach was non-inferior to the CAD4TBv7 approach (non-inferiority margin –10%) and to conduct a comparative cost analysis between the two approaches.

Findings Among 20 023 enrolled participants, the median age was 42 years (IQR 29–60); 12 387 (61·9%) participants were female, 7625 (38·1%) were male, and 11 (0·1%) were intersex. 4534 (22·6%) of 20 023 participants were living with HIV, 1547 (7·7%) had a history of tuberculosis, and 1545 (7·7%) reported at least one of the four main symptoms of tuberculosis. The primary outcome set, defined as participants who were identified as having tuberculosis according to at least one of the two approaches and had complete data for both approaches, comprised 73 participants: the CAD4TBv7 approach identified 69 (94·5%) of these cases of tuberculosis and the CAD4TBv7-CRP approach identified 60 (82·2%) cases. The difference of –12·3% (95% CI –23·0 to –1·6) indicates that the non-inferiority criterion was not met. The cost per detected case of tuberculosis was US$5454 (95% uncertainty interval 4294–6777) for the CAD4TBv7 approach and $7486 (5948–9246) for the CAD4TBv7-CRP approach, making the CAD4TBv7-CRP approach 37·3% more expensive.

Interpretation In active tuberculosis case-finding in our community setting, the combination of CAD followed by CRP testing offered no advantage over CAD alone owing to its inferior case yield and higher cost. CAD alone, however, has the potential to be an effective and economically viable tuberculosis screening strategy in areas with high disease burden.

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Introduction

Tuberculosis is a global health threat.[1] One in four cases of active tuberculosis is either undiagnosed or unreported, leading to longer infectiousness and transmission periods, high risk of unfavourable outcomes, and adverse economic consequences for both individuals and health systems.[2–4] National tuberculosis control programmes rely mainly on passive case-finding, which could miss opportunities for the early diagnosis and treatment of vulnerable populations, who often face social, economic, or geographical barriers to accessing health care,[5] or individuals with asymptomatic tuberculosis, who account for around 50% of microbiologically confirmed cases of tuberculosis in communities.[6]

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Research in context

Evidence before this study

In 2021, WHO recommended computer-aided detection (CAD) for tuberculosis screening in individuals aged 15 years or older, and C-reactive protein (CRP) testing in addition to the WHO-recommended four-symptom screen for tuberculosis screening in people living with HIV. Little research has been conducted on combining these tools in the context of community-based tuberculosis screening. We searched PubMed, using the search terms ("TB" OR "tuberculosis") AND ("computer aided detection" OR "computer assisted diagnosis" OR "artificial intelligence") AND ("C-reactive protein" OR "CRP") AND ("active case finding" OR "screening"), for records published between database inception and Jan 31, 2026, with no restrictions on language or article type. This search returned eight records. A community study from Zambia and South Africa, nested within a prevalence survey, investigated the diagnostic accuracy of CRP testing and four serial and parallel screening algorithms, of which two included CAD. A community trial in people who inject drugs from Viet Nam investigated the accuracy, case yield, and cost of algorithms for CAD but not for CRP testing. The remaining publications comprised a review; a head-to-head comparison of triage tests in primary health care; a prospective household contact study on the performance of CAD, in which CRP testing was conducted only in a subgroup of participants; a study on point-of-care ultrasound with CRP testing as one comparator; a case report; and the study protocol for the current trial. These search results indicate that little data are available comparing CAD alone with the combination of CAD and CRP testing in the early detection of tuberculosis in communities with a high case burden.

Added value of this study

To our knowledge, this is the first pragmatic, symptom-agnostic community trial that compares CAD alone with CAD followed by CRP testing (for participants with CAD scores within a particular range) in terms of tuberculosis case yield and cost. Unlike studies at health-care facilities, tuberculosis screening in the community is complicated by relatively low disease prevalence and the requirement for detection in the early stages of disease. In addition, community campaigns place high logistical and financial demands on resources. For this reason, the coprimary endpoints of this trial, which used a paired screen-positive design (ie, within-person comparison), involved both tuberculosis case yield and cost-effectiveness or, if one approach was inferior in terms of tuberculosis case yield, costs. Contrary to the original trial hypothesis, we found that CAD alone identified more tuberculosis cases in the communities at lower costs; the use of CRP testing in combination with CAD did not result in any operational or financial advantages in our trial. Furthermore, a cost analysis showed that the average cost per detected case of tuberculosis was lower for CAD than in scenarios in which Xpert MTB/RIF Ultra testing was used for all participants, although fewer confirmed cases were identified.

Implications of all the available evidence

Our trial adds evidence in support of the implementation of CAD for symptom-agnostic community tuberculosis screening. Our findings suggest that the use of CAD followed by CRP testing does not have any advantage over the use of CAD alone, at least in similar contextual settings. The data on tuberculosis case yield and the cost analyses are relevant for the design and realisation of tuberculosis screening campaigns by key stakeholders—such as policy makers, national tuberculosis programmes, and community organisations—and could contribute to the improved identification of tuberculosis beyond the currently prevailing passive case-detection strategies.

Consequently, WHO recommends active tuberculosis case-finding strategies in the general population when the estimated prevalence is at least 0·5%, or in subpopulations with a high risk of tuberculosis, such as people who might be underserved, household contacts of people with tuberculosis, people living with HIV, migrants, people who are incarcerated, or people who work as miners.[7] Active case-finding strategies should be carefully planned, be logistically and economically feasible, and use tools with at least 90% sensitivity and at least 70% specificity, as per the WHO target product profile at the time of this trial.[8]

Computer-aided detection (CAD) of tuberculosis-related pathologies on chest radiographs and the measurement of C-reactive protein (CRP) blood concentrations are among the most promising tuberculosis screening tools.[9,10] For screening, WHO recommends CAD as an alternative to human analysis of digital chest x-rays and CRP assays as a test for tuberculosis in adolescents and adults living with HIV.[7] CAD uses artificial intelligence-powered software to analyse digital chest x-rays and provide an abnormality score; higher scores suggest a higher likelihood of pulmonary tuberculosis. The performance of current CAD software is at least similar to that of human experts,[9,11] making CAD particularly relevant for settings in which the availability of radiologists is limited. CRP is an acute phase marker of inflammation and infection and can be measured at the point of care; however, such assays do not meet WHO's target product profile criteria as a standalone tool in community screening.[12]

Data on the utility and costs of a community approach that combines CAD with CRP testing are scarce. We conducted a pragmatic trial to compare screening using CAD alone (termed the CAD4TBv7 approach) with screening using CAD combined with point-of-care CRP testing (termed the CAD4TBv7-CRP approach) in communities in South Africa and Lesotho. We used a paired screen-positive design (ie, using within-person comparison) to test the hypotheses that, compared with the CAD4TBv7 approach, the CAD4TBv7-CRP approach

is non-inferior in terms of effectiveness (ie, tuberculosis case yield) and superior in terms of cost-effectiveness. If the effectiveness hypothesis was not supported, we planned to conduct a comparative cost analysis instead of a cost-effectiveness analysis.

Methods

Study design and participants

The TB TRIAGE+ trial was a prospective, community-based, diagnostic, pragmatic trial with a paired screen-positive design,[13] in which all participants underwent both of two population-based screening approaches to gain statistical efficiency.[14]

The trial took place in South Africa and Lesotho, countries with high rates of tuberculosis and HIV: in 2024, the estimated incidence of tuberculosis per 100 000 population was 389 in South Africa and 548 in Lesotho.[1] The trial was conducted in three neighbourhoods within the semi-rural Greater Edendale area of Msunduzi Municipality (uMgungundlovu District) in South Africa and in 182 villages in the predominately rural Butha-Buthe District in Lesotho. Neighbourhoods or villages representing the sampling units met predetermined criteria, as per the study protocol,[14] and were selected by simple random sampling by an independent statistician using Stata software.

Household members aged 18 years or older were eligible to participate. Individuals were excluded if they were seriously ill or if they had any condition for which participation in the trial could have compromised their wellbeing or prevented, limited, or confounded protocol-specified assessments. Individuals undergoing tuberculosis treatment were excluded (preventive tuberculosis treatment was permissible). In Lesotho, self-reported pregnancy was an exclusion criterion. At enrolment, we collected self-reported data on the participants' demographic characteristics (eg, age, sex at birth), clinical symptoms, medical history, tuberculosis risk profile, and concomitant medication, as described in the study protocol.[14]

Permission for the screening campaign was obtained from the village authorities or community advisory boards. Written informed consent, or witnessed oral consent in the case of illiteracy, was obtained from all participants before any trial procedure.

The trial was approved by the National Health Research Ethics Committee in Lesotho (ID52–2022) and by the Human Sciences Research Council Research Ethics Committee (REC 2/23/09/20) and the Provincial Health Research Committee of the Department of Health of KwaZulu-Natal (KZ_202209_022) in South Africa. The Ethikkommission Nordwest- und Zentralschweiz in Switzerland confirmed that ethical requirements were met (AO_2022–00044). The trial was registered with the South African National Clinical Trials Register (DOH-27-092022-8096) and at ClinicalTrials.gov (NCT05526885).

Procedures

All participants received a posterior–anterior digital chest x-ray, which was analysed using CAD4TBv7 software (Delft Imaging Systems, 's-Hertogenbosch, Netherlands). A stationary x-ray system (Fujifilm FDR Smart with FXRD 1717V panel detector; Fujifilm, Tokyo, Japan) on a mobile trailer was deployed in South Africa, whereas a portable system (Delft Light with Canon CXDI-70 panel detector; Delft Imaging Systems, 's-Hertogenbosch, Netherlands) was used in Lesotho.

Two screening approaches were compared, in which predefined thresholds (t) were used (figure 1).[14] In the CAD4TBv7 approach, participants with a CAD score less

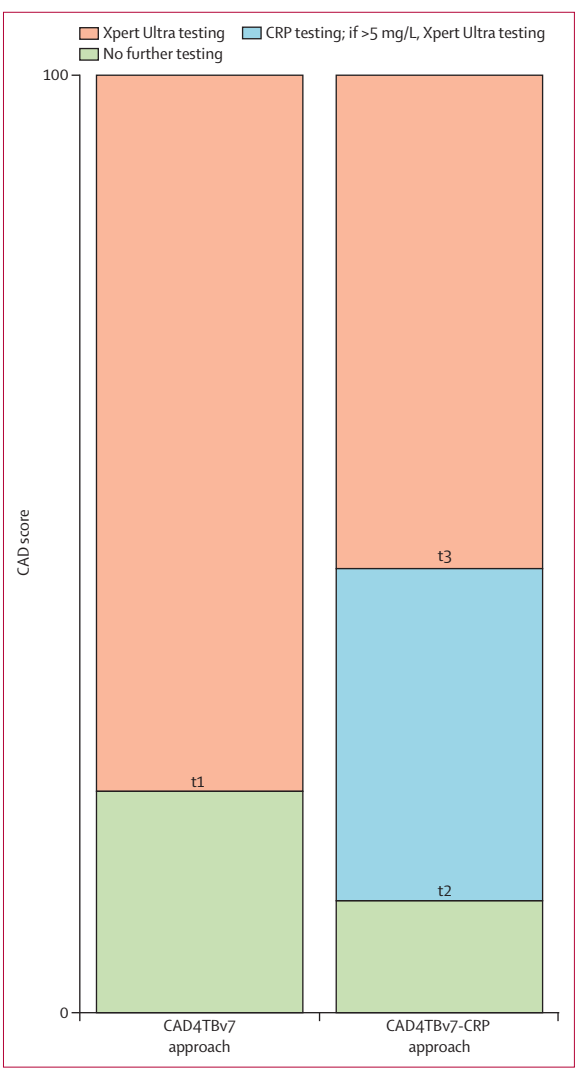

Figure 1: **Trial design**
The numerical values of the thresholds per country are shown in the appendix (p 10). CAD=computer-aided design. CRP=C-reactive protein. t1=CAD score threshold with sensitivity of at least or close to 90%. t2=CAD score threshold with sensitivity of at least or close to 95%. t3=CAD score threshold with specificity of at least or close to 95%. Xpert Ultra=Xpert MTB/RIF Ultra. Adapted by permission from BMJ Publishing Group. *BMJ Open*, Signorell A, van Heerden A, Ayakaka I, et al, 15, e093989, 2025.

than or equal to t1 (cutoff with sensitivity of at least or close to 90%) were considered tuberculosis screen-negative, whereas those with a CAD score greater than t1 received a confirmatory Xpert MTB/RIF Ultra (hereafter Xpert Ultra) test (Cepheid, Sunnyvale, CA, USA). In the CAD4TBv7-CRP approach, participants with a CAD score less than or equal to t2 (cutoff with sensitivity at least or close to 95%) were considered tuberculosis screen-negative. If the CAD score was greater than t3 (cutoff with a specificity at least or close to 95%), a confirmatory Xpert Ultra test was conducted. If, in this approach, the CAD score was within a specific window (>t2 and ≤t3), a CRP test (LumiraDX, Stirling, UK) was conducted using capillary blood. A confirmatory Xpert Ultra test was conducted if the CRP concentration was greater than 5 mg/L; otherwise, these participants were considered tuberculosis screen-negative. Positive Xpert Ultra results were considered confirmatory, whereas trace results were not taken into account for trial outcomes.

As described in the protocol,[14] CAD score thresholds had to be redetermined in the initial phase of the trial because the distribution of scores was highly dependent on the radiological equipment used.[15] To determine the final thresholds, we used datasets from preceding community-based tuberculosis surveys and studies: the 2019 National Tuberculosis Prevalence Survey in Lesotho[16] used similar equipment to our South African site, whereas devices used in a study by the Vukuzazi Team[17] corresponded to those at our Lesotho site (appendix p 10). Appropriate statistical methods were used to account for the large proportion of unknown tuberculosis cases due to the recruitment logic of the surveys.[18]

See Online for appendix

All data were captured electronically. Sputum samples for liquid culture were additionally collected from asymptomatic participants with a positive result on the Xpert Ultra test (including those with a trace result). We conducted the following tests for chronic diseases: HIV testing and additional tuberculosis testing according to national HIV guidelines, the advanced HIV disease package of care (ie, CD4 cell count, cryptococcal antigen test, and TB-LAM antigen test) as per WHO guidelines,[19] glycated haemoglobin (HbA_{1c}) testing for participants aged 45 years or older or with an elevated waist circumference (≥94 cm for male participants and ≥80 cm for female or intersex participants), and blood pressure measurement as per the WHO STEPS protocol.[20] We also collected information from participants on past and current tobacco use and assessed their risk of unhealthy alcohol use with the Alcohol Use Disorders Identification Test (AUDIT-C; at-risk scores ≥4 for male participants and ≥3 for female participants; intersex participants were not included in this analysis).[21]

Participants were referred to the nearest health-care facility for further investigations and treatment according to national guidelines if they had a tuberculosis-positive test or if they had a trace result on the Xpert Ultra test, which was not considered a positive confirmatory test. The study teams could, based on their expertise, classify a participant as having clinical or radiological suspected tuberculosis and refer them for further assessment as per the national standard of care. Individuals with elevated HbA_{1c} values (≥6·5%, ≥48 mmol/mol) or elevated blood pressure (systolic ≥140 mm Hg and/or diastolic ≥90 mm Hg) were referred for further investigation of these conditions. Participants eligible for same-day antiretroviral therapy, cotrimoxazole prophylaxis, and/or tuberculosis prevention therapy received medication for 2–4 weeks and were referred.

At day 56 (±6 days), information was collected via a household visit or telephone call from the following participants: those with tuberculosis confirmed by an Xpert Ultra test, TB-LAM antigen testing, or culture; those with a trace result on the Xpert Ultra test; those with clinical or radiological suspicion of tuberculosis as judged by the study team; those who were unable to produce a required sputum sample; those with advanced HIV disease; those with newly diagnosed HIV infection at screening (as per national guidelines); or those who were living with HIV and who interrupted antiretroviral therapy. Data on tuberculosis diagnoses and treatment since enrolment were collected from the tuberculosis registers for participants with a positive or trace result on the Xpert Ultra test, TB-LAM-positive participants, and participants with a clinical or radiological suspicion of tuberculosis as judged by the study team (including those with CAD scores and/or CRP concentration above threshold). Data on HIV diagnoses and treatment were obtained from HIV registers for individuals with advanced HIV disease and confirmed or suspected tuberculosis with HIV infection.

Safety information—comprising adverse events, serious adverse events, and incidental findings—was collected on the day or days of the community-based study procedures by solicitation from, observation of, and/or reporting by the study participant. Risk-based trial monitoring was provided by the independent Clinical Operations Unit of the Swiss Tropical and Public Health Institute.

Outcomes

The primary objective was to test the hypothesis that the CAD4TBv7-CRP approach would not lead to reduced community tuberculosis case detection (defined as a positive result on the Xpert Ultra test, disregarding trace results) compared with the CAD4TBv7 approach (non-inferiority) and that the CAD4TBv7-CRP approach would be more cost-effective than the CAD4TBv7 approach (superiority). The rationale was that CRP testing could potentially be used to reduce the number of expensive Xpert Ultra tests required without compromising the tuberculosis case-detection rate. If non-inferior effectiveness of the CAD4TBv7-CRP approach was not shown, a comparative cost analysis was planned instead

of a cost-effectiveness analysis. Primary outcome measures were the number of tuberculosis cases detected, the costs per tuberculosis case detected, the total costs of tuberculosis screening, and the cost per participant screened.

The secondary objectives included the comparison of costs with a hypothetical approach in which all participants underwent Xpert Ultra testing (termed Xpert Ultra in all) in three scenarios with different population sizes (post-hoc; appendix pp 16–25). A full list of secondary objectives can be found in the study protocol.[14] Secondary outcome measures included the costs per tuberculosis case detected, the total costs of tuberculosis screening, the cost per participant screened, the number of participants with diagnosed tuberculosis, the incremental cost per additional tuberculosis case detected compared with the CAD4TBv7 approach, and costs for the hypothetical scenarios.

Statistical analysis

The sample size calculation was based on simulations with a non-inferiority margin of 10%, yielding a size of 20 000 participants (appendix pp 14–15). Participant characteristics and screening were summarised by country, and tuberculosis case yields by screening approach. For the primary effectiveness non-inferiority comparison, CIs were estimated under an asymptotic assumption and accounting for the paired nature of the observations (appendix pp 14–15). Non-inferiority in terms of tuberculosis case yield would be shown if the lower bound of the two-sided 95% CI was greater than –10%. Further, we estimated the relative sensitivity (ie, the relative true positive rate) using marginal log-linear models estimated with generalised estimating equations, adjusted for country.[22] Effect modification of the first coprimary outcome was assessed descriptively by country, HIV status, age, history of tuberculosis, and tuberculosis symptoms. Pre-planned sensitivity analyses were including trace results from the Xpert Ultra test as part of the tuberculosis case definition among those with no tuberculosis history; including trace results from the Xpert Ultra test as part of the tuberculosis case definition regardless of tuberculosis history; using alternative CRP thresholds of at least 7 mg/L and at least 10 mg/L; and assuming that all participants from Lesotho who enrolled during the initial phase of the trial (before the threshold redetermination) and had a CAD score greater than 44 and less than or equal to 50, therefore did not have CRP tested under the initial algorithm (but should have had CRP tested under the redetermined algorithm), would have had CRP concentrations of greater than 5 mg/L.

In the case that the CAD4TBv7-CRP approach was found to be non-inferior to the CAD4TBv7 approach, a cost-effectiveness analysis for superiority was planned as the second coprimary endpoint under intention-to-test principles. In the case that non-inferiority was not shown, we planned to conduct a costing analysis instead (appendix pp 16–18).

The full analysis set was predefined as all eligible, consenting, and enrolled participants, excluding those for whom technical problems were encountered during use of the x-ray device or during image acquisition and those who were receiving undisclosed treatment for tuberculosis at the time of the study procedures. Participant characteristics and costs were analysed in the full analysis set. The primary outcome set was defined as participants from the full analysis set who had complete data for both screening approaches (CAD4TBv7 and CAD4TBv7-CRP), who were identified through either of these two approaches (based on data captured at enrolment only) to be eligible for an Xpert Ultra test, and who had a positive result for this test.

The primary effectiveness outcome was analysed using the primary outcome set. Statistical analyses were conducted using Stata (version 18) and R software (version 4.4.1).

The primary cost analysis adopted a programmatic perspective, considering costs related to routine tuberculosis screening while excluding costs related to research, HIV, or chronic disease care. The cost analysis involved a bottom-up, ingredients-based approach, capturing both capital costs (eg, medical and diagnostic equipment and vehicles) and recurrent programmatic costs (eg, personnel, diagnostic test kits and cartridges, consumables, and fuel), therefore reflecting the full resource requirements of operating a community-based screening campaign. Cost data were collected prospectively during implementation and retrospectively from project financial records (appendix pp 16–19).

Post-hoc cost analyses were conducted under the assumption that all participants were tested with the Xpert Ultra test. In three scenarios, the Xpert Ultra in all approach was compared with the screening approaches investigated in the trial. (appendix pp 16–21).

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

14 042 households were enumerated comprising 53 474 household members, of whom 21 391 were younger than 18 years and therefore not eligible for the study. Of the 32 083 adult household members, 11 623 (36·2%) did not present or were not enrolled (median age 35 years [IQR 25–49]; 6127 [53·1%] were male, 5405 [46·8%] were female, nine [0·1%] were intersex, and 82 had missing sex information): 11 618 (>99·9%) were absent, one (<0·1%) was in a critical condition, and four (<0·1%) were receiving treatment for tuberculosis. No household members who were present and eligible declined to participate (figure 2). 20 460 adults provided informed

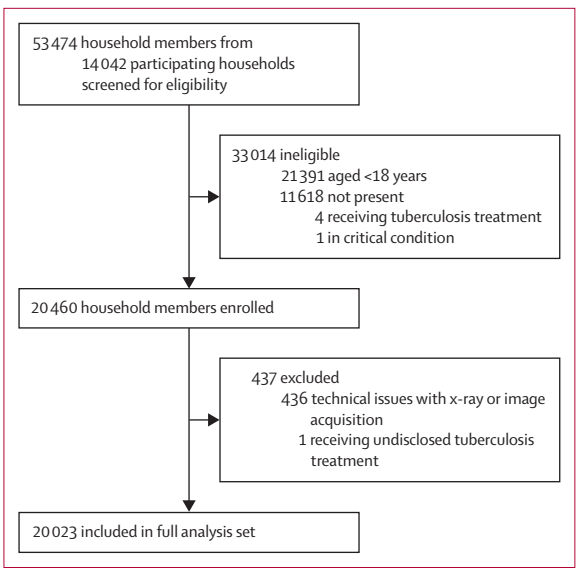

Figure 2: **Trial profile**

consent and were enrolled between Sept 26, 2022, and Sept 4, 2024. After exclusion of participants because of technical problems with an x-ray device or image acquisition (n=436) or because of undisclosed treatment for tuberculosis (n=1), 20 023 adults were included in the full analysis set: 6986 (34·9%) in South Africa and 13 037 (65·1%) in Lesotho (table 1).

The median age of the 20 023 enrolled participants was 42 years (IQR 29–60); 12 387 (61·9%) were female, 7625 (38·1%) were male, and 11 (0·1%) were intersex. 1545 (7·7%) participants reported at least one of the main tuberculosis symptoms (adapted from the WHO-recommended four-symptom screen):[7] fever, cough of any duration, weight loss, or night sweats. The most frequently reported symptom, in 1313 (6·6%) of 20 023 participants, was cough of any duration. 4534 (22·6%) of 20 023 participants were living with HIV, of whom 61 (1·3%) were newly diagnosed at enrolment. 4451 (98·2%) of 4534 participants living with HIV reported taking antiretroviral therapy at the time of enrolment, and 22 (0·5%) of 4534 participants were known to be HIV positive but were not on antiretroviral therapy at the time of enrolment. 1547 (7·7%) of 20 023 participants reported a history of tuberculosis, 1325 (6·6%) had worked as miners, 219 (1·1%) had a household member who currently or had previously had tuberculosis, 736 (3·7%) reported having diabetes, and 1039 (5·2%) had increased HbA_{1c} concentrations. Of the 20 023 participants, a history of tobacco use was reported by 5618 (28·1%), and 4161 (20·8%) were at risk of unhealthy alcohol use according to the AUDIT-C score.[21] An elevated blood pressure was measured in 2365 (11·8%) participants.

All but one (6985, 100·0%) of 6986 participants in South Africa and 12 724 (97·6%) of 13 037 participants in Lesotho received a chest x-ray and a CAD score. The distribution of CAD scores differed between countries (appendix pp 3, 11). Under the CAD4TBv7 approach, 650 (9·3%) of 6985 participants in South Africa and 3841 (30·2%) of 12 724 participants in Lesotho had CAD scores above the threshold for an Xpert Ultra test. Under the CAD4TBv7-CRP approach, 1166 (16·7%) of 6985 participants in South Africa and 5892 (46·3%) of 12 724 participants in Lesotho had CAD scores within the defined window for a CRP test. The results of CRP tests were similarly distributed in both countries: 32·6% of participants in South Africa (377 of 1158; eight results missing) and 27·2% of participants in Lesotho (1498 of 5489; 403 results missing) had CRP concentrations greater than 5 mg/L. Further, under this approach, 225 (3·2%) of 6985 participants in South Africa and 672 (5·3%) of 12 724 participants in Lesotho had CAD values above the threshold for a direct Xpert Ultra test without CRP testing. Results of Xpert Ultra tests according to CAD scores and CRP test results are shown in the appendix (p 3).

The primary outcome set comprised 73 participants: those who were identified as having tuberculosis according to at least one of the two approaches and had complete data for both approaches. The CAD4TBv7 approach detected 69 (94·5%) of the 73 cases of tuberculosis among participants, whereas the CAD4TBv7-CRP approach identified 60 (82·2%) of the 73 cases (tables 2, 3). These findings yielded an absolute difference of –12·3% (two-sided 95% CI –23·0 to –1·6) in the proportion of tuberculosis cases identified by the two approaches. As the lower bound of the CI was below the non-inferiority margin of –10%, the non-inferiority criterion was not met; in fact, the findings show that the CAD4TBv7-CRP approach performed significantly worse than the CAD4TBv7 approach (appendix p 13). The relative sensitivity (ie, the ratio of the sensitivities under the CAD4TBv7-CRP approach *vs* the CAD4TBv7 approach), adjusted for country, was 0·86 (95% CI 0·76–0·98). These differences in tuberculosis case yield between the approaches were robust to predefined sensitivity analyses (appendix pp 5–6). We observed no noticeable effect modification by country, HIV status, age, and tuberculosis symptoms; there was some indication that the CAD4TBv7-CRP approach might have better performance than the CAD4TBv7 approach among people with a history of tuberculosis, although the number of observations was small and therefore these results should be interpreted cautiously (appendix pp 7–9). Among the 73 participants in the primary outcome set, tuberculosis was exclusively detected by the CAD4TBv7 approach in 13 participants and by the CAD4TBv7-CRP approach in four participants (table 3).

The primary cost analysis was based on 76 participants with tuberculosis from the full analysis set of 20 023 participants, namely, the primary outcome set of 73 participants with tuberculosis plus an additional

	South Africa (n=6986)	Lesotho (n=13 037)	Total (N=20 023)
Age, years	35 (26–49)	46 (31–64)	42 (29–60)
Sex at birth (self-reported)			
Female	3803 (54·4%)	8584 (65·8%)	12 387 (61·9%)
Male	3177 (45·5%)	4448 (34·1%)	7625 (38·1%)
Intersex	6 (0·1%)	5 (<0·1%)	11 (0·1%)
Symptoms			
Any of the main tuberculosis symptoms*	614 (8·8%)	931 (7·1%)	1545 (7·7%)
Cough of any duration	482 (6·9%)	831 (6·4%)	1313 (6·6%)
Weight loss	100 (1·4%)	108 (0·8%)	208 (1·0%)
Night sweats	67 (1·0%)	80 (0·6%)	147 (0·7%)
Fever	34 (0·5%)	46 (0·4%)	80 (0·4%)
Chest pain	51 (0·7%)	169 (1·3%)	220 (1·1%)
Fatigue	23 (0·3%)	91 (0·7%)	114 (0·6%)
HIV status (reported or newly diagnosed)			
Living with HIV	1968 (28·2%)	2566 (19·7%)	4534 (22·6%)
No evidence of HIV or unknown HIV status	5018 (71·8%)	10 471 (80·3%)	15 489 (77·4%)
Medical and occupational history			
History of tuberculosis at any time	800 (11·5%)	747 (5·7%)	1547 (7·7%)
Worked as a miner	88 (1·3%)	1237 (9·5%)	1325 (6·6%)
Household contact with current or previous tuberculosis	100 (1·4%)	119 (0·9%)	219 (1·1%)
Diabetes	268 (3·8%)	468 (3·6%)	736 (3·7%)
Ever smoked	2364 (33·8%)	3254 (25·0%)	5618 (28·1%)
At risk of unhealthy alcohol use†	1869 (26·8%)	2292 (17·6%)	4161 (20·8%)
Study measurements			
HbA_{1c} ≥6·5%‡	342 (4·9%)	697 (5·3%)	1039 (5·2%)
Elevated blood pressure§	361 (5·2%)	2004 (15·4%)	2365 (11·8%)
Waist circumference, cm	78 (72–86)	82 (76–93)	80 (75–91)

Data are median (IQR) or n (%). The proportion of missing results was less than 1% for each variable, except for household contact with current or previous tuberculosis (missing results, refused, or unknown: 3991 [19·9%] in total, 1720 [24·6%] in South Africa, and 2271 [17·4%] in Lesotho) and HbA_{1c} ≥6·5% (missing results for participants with indication for HbA_{1c} testing: 1756/11 401 [15·4%] in total, 351/2506 [14·0%] in South Africa, and 1405/8895 [15·8%] in Lesotho). AUDIT-C=Alcohol Use Disorders Identification Test. HbA_{1c}=glycated haemoglobin. *Cough of any duration, weight loss, night sweats, and fever (WHO-recommended four-symptom screen). †Determined by AUDIT-C score of ≥4 for male participants and ≥3 for female participants; intersex participants were not included in this analysis. ‡Participants eligible for an HbA_{1c} test were those aged ≥45 years or with a waist circumference of ≥94 cm for male participants and ≥80 cm for female or intersex participants. §Defined as a systolic blood pressure of ≥140 mm Hg and/or a diastolic blood pressure of ≥90 mm Hg (mean of triplicate measurements).[20]

Table 1: **Demographic and clinical characteristics**

three participants with tuberculosis from Lesotho who were enrolled under the initial algorithm before CAD score redetermination and had incomplete data for the CAD4TBv7-CRP approach. The CAD4TBv7-CRP approach was dominated by the CAD4TBv7 approach, being both more costly and detecting fewer tuberculosis cases. The average cost per case of tuberculosis detected was US$5454 (95% uncertainty interval [UI] 4294–6777) for the CAD4TBv7 approach and $7486 (5948–9246) for the CAD4TBv7-CRP approach—ie, the CAD4TBv7-CRP approach was 37·3% more expensive than the CAD4TBv7 approach (table 4). For both approaches, the average cost per case of tuberculosis detected was higher in Lesotho than in South Africa: $5987 (4740–7411) versus $4749 (3704–5939) for the CAD4TBv7 approach and $8544 (6842–10 444) versus $6356 (4993–7964) for the CAD4TBv7-CRP approach. The cost per person screened was $20 (15–24) for the CAD4TBv7 approach and $22 (18–28) for the CAD4TBv7-CRP approach. The total cost of the tuberculosis screening activities in the study population was $392 695 (309 144–487 934) for the CAD4TBv7 approach and $449 175 (356 894–554 738) for the CAD4TBv7-CRP approach (table 4).

The post-hoc cost analysis showed that, for the trial population with the observed prevalence, the average cost per case of tuberculosis detected by a hypothetical Xpert Ultra in all approach was $6961 (95% UI

	CAD4TBv7 approach	CAD4TBv7-CRP approach	Mean difference (two-sided 95% CIs)
Primary outcome set*			
Tuberculosis cases detected†	69	60	..
Proportion of detected cases	94·5%	82·2%	−12·3% (−23·0 to −1·6)
Full analysis set‡			
Tuberculosis cases detected	72	60	..
Tuberculosis prevalence	0·4%	0·3%	..

CAD=computer-aided detection. CRP=C-reactive protein. *Comprises only participants with complete data from both approaches. †Detected either by one approach or both, and having complete data for both approaches (n=73). ‡Participants with data from only one approach are also included (ie, an additional three participants who were identified as having tuberculosis by the CAD4TBv7 approach but who had missing CRP testing data, therefore incomplete data for the CAD4TBv7-CRP approach, are included; n=76).

Table 2: **Tuberculosis case yield in the primary outcome and full analysis sets**

	Tuberculosis case under CAD4TBv7-CRP approach		
	No	Yes	Total
Tuberculosis case under CAD4TBv7 approach			
No	..	4 (5·48%)	4 (5·48%)
Yes	13 (17·81%)	56 (76·71%)	69 (94·52%)
Total	13 (17·81%)	60 (82·19%)	73 (100%)

Table 3: **Two-by-two table of tuberculosis case yield in the primary outcome set**

	CAD4TBv7 approach	CAD4TBv7-CRP approach	Percentage difference between cost of CAD4TBv7-CRP approach and cost of CAD4TBv7 approach
Cost per tuberculosis case detected, US$	5454 (4294–6777)	7486 (5948–9246)	37·3%
Total cost of tuberculosis screening, US$	392 695 (309 144–487 934)	449 175 (356 894–554 738)	14·4%
Cost per participant screened, US$	20 (15–24)	22 (18–28)	10·0%

Data are estimate (95% UI) and are economic costs presented in 2023 US dollars. Based on the prevalence of tuberculosis observed in the trial. Screening for HIV and non-communicable diseases was not included in the cost analysis. A coefficient of variation of 20% was assumed and a 95% UI was calculated in line with WHO-CHOICE guidelines,[23] using the full analysis set. UI=uncertainty interval.

Table 4: **Cost analysis**

5323–8920), in between the costs of the two approaches in the trial (appendix pp 22–25).

In addition to the 76 participants with tuberculosis in the full analysis set, two additional participants were identified as having tuberculosis at enrolment: one who received only an Xpert Ultra test (and had a positive result) based on the thresholds of the initial, later revised algorithm used in Lesotho; and one who was living with HIV and had a positive TB-LAM test (appendix p 4). Among these 78 participants, 70 (90%) were receiving tuberculosis treatment at day 56 (self-reported and/or registered), four (5%) had been referred but were not on treatment at day 56, no referral documental was found for three (4%) participants, and one (1%) participant refused referral. Three participants had rifampicin-resistant tuberculosis.

35 participants had trace results on the Xpert Ultra test, of whom 16 (46%) did not have any of the four main tuberculosis symptoms and 14 (40%) had a history of tuberculosis. Of these 35 participants, 21 (60%) had a second Xpert or Xpert Ultra test at a health facility and received a positive result, all of whom were on treatment at day 56. A further seven (20%) participants were on tuberculosis treatment at day 56 without a second confirmatory test, three (9%) were referred but not on treatment at day 56, and four (11%) had no documented referral. The characteristics and treatment status of participants with trace results on the Xpert Ultra test are shown in the appendix (p 13). One participant whose culture became positive after enrolment reported at follow-up receiving tuberculosis treatment, but no corresponding record of this treatment could be found. Xpert Ultra testing was required according to at least one of the screening algorithms in 5405 participants, among whom results were missing for 114 (2·1%): 46 participants were unable to produce sputum, 49 withdrew from the study or refused to provide a sputum sample, and for 19 participants there were other reasons for not collecting sputum. Sputum samples for liquid culture were collected from 48 of the 50 asymptomatic participants with positive or trace results from the Xpert Ultra test: 15 were positive, 31 were negative, one had non-tuberculous mycobacteria, and one was contaminated.

In summary, by day 56, 100 (0·5%) of 20 023 participants had microbiologically confirmed tuberculosis, among whom 46 (46·0%) had none of the four main tuberculosis symptoms. Moreover, the study team classified 102 participants as having clinical symptoms or radiological signs suggestive of tuberculosis (79 participants with clinical suspicion only, 22 with radiological suspicion only, and one with both; these numbers do not include participants who were referred because of positive or trace results on Xpert Ultra tests, or those for whom Xpert Ultra tests were required but missing). This assessment was often revised after consultation with a study doctor, a process that was not always accurately captured in the study documentation. At day 56, 86 (84%) of the 102 participants with clinical symptoms or radiological signs suggestive of tuberculosis were reachable, all of whom reported no tuberculosis treatment since enrolment.

No adverse events were reported at either of the two sites during the community visits.

Discussion

To our knowledge, this is the first large-scale pragmatic trial to compare the diagnostic yield and the cost of CAD alone (CAD4TBv7 approach) versus CAD combined with CRP testing (CAD4TBv7-CRP approach) as tuberculosis screening approaches in community settings with high prevalences of tuberculosis and HIV.

In our trial, we did not show non-inferiority of the CAD4TBv7-CRP approach compared with the CAD4TBv7 approach. Indeed, the CAD4TBv7-CRP approach detected fewer tuberculosis cases and was more expensive at identifying tuberculosis at the community level than the CAD4TBv7 approach. Specifically, the CAD4TBv7 approach identified 15% more individuals with active tuberculosis under trial conditions, and as many as 20% more when participants with data from only one approach were also included. Our findings in terms of tuberculosis case yield were not influenced by including or excluding individuals with trace results on the Xpert Ultra test, nor by using different CRP thresholds. Moreover, country, age, HIV status, or reporting a tuberculosis symptom did not affect this outcome. The trial data, generated in a specific context, suggest that a combination of CAD and CRP testing offers no advantages for tuberculosis screening in the communities, neither in terms of yield nor cost. The low case yield is in line with those of other community studies, with different designs to ours, which

showed that the diagnostic accuracy of CRP testing does not meet WHO target product profile criteria for tuberculosis screening. However, these studies suggested that CRP testing could be potentially beneficial owing to its low cost and ease of availability, with higher sensitivity among people most likely to be contagious[24] or when combined in parallel with symptom screening.[12] A facility-based multicentre study reported improved accuracy when CAD followed CRP testing in sequential negative serial screening.[25] However, the results of that study are not comparable with ours, as the study used a different two-step approach and was conducted on symptomatic individuals who visited health-care facilities.

The prevalence of confirmed tuberculosis among the study participants was 0·5%, which is lower than estimates from tuberculosis prevalence surveys in Lesotho and South Africa.[16,26] However, our trial was not designed to provide a representative sample of the population. In addition, the focus on rural areas, which usually have a lower-than-average tuberculosis prevalence, and the high absence rate among male household members, who typically have a higher burden of disease than female members, might have contributed to the lower prevalence rates.

Given the complexity and scale of active case-finding campaigns, identifying the most cost-saving approach is crucial to ease the economic burden on health systems. The CAD4TBv7-CRP approach was more expensive than the CAD4TBv7 approach and was also more expensive than the simulated Xpert Ultra in all approach, arguing against its wider implementation. The average cost per case of tuberculosis detected was 37·3% higher for the CAD4TBv7-CRP approach than for the CAD4TBv7 approach. In all participants, this difference was 14·4% in terms of total costs and 10·0% in terms of cost per participant screened. The number of Xpert Ultra tests averted through CRP triage was insufficient to offset the additional costs associated with the CAD4TBv7-CRP approach, particularly the high cost of medical equipment (eg, CRP tests) and the personnel required to operate it. The interpretation of the post-hoc cost analyses is detailed in the appendix (pp 22–25).

Despite the redetermination of the CAD thresholds using external datasets to adjust for the dependency of CAD score distribution on x-ray hardware,[15] differences remained in the distribution of CAD scores and therefore the subsequent number of CRP tests conducted, which partly explains the higher average cost per tuberculosis case detected in Lesotho than in South Africa. To avoid potential bias, the use of x-ray data from previous datasets, as recommended by WHO for CAD,[27] seems to be appropriate only if identical x-ray machines are used or if the CAD score distributions are sufficiently similar. Besides, considering population characteristics is essential when determining CAD thresholds.

Initially, 35 participants had a trace result on the Xpert Ultra test, after which they were referred to a health facility as per WHO recommendations.[28] Similar to the findings of a community-based active case-finding study in Viet Nam,[29] the proportion of these participants who were subsequently confirmed as having and were treated for tuberculosis was high, at 60% (21 of 35). Because trace results contribute substantially to the number of confirmed cases of tuberculosis, it is advisable to integrate necessary follow-up testing into active case-finding campaigns to avoid attrition and to ensure that the overall case yield is reported accurately.

Furthermore, 46% of participants with confirmed tuberculosis had none of the main tuberculosis symptoms, which is consistent with previous results from surveys and studies.[6,30] Symptom-agnostic active case-finding is the most effective strategy for detecting asymptomatic tuberculosis. Early linkage to care benefits both the individual, who will have a better chance of survival and fewer sequelae,[4] and society, as subclinical tuberculosis is thought to contribute to community transmission.[31]

Our trial has several strengths, including the paired screen-positive design, which enabled us to examine the two screening approaches in the same person. Compared with a cluster-randomised trial, the paired screen-positive design is more efficient, achieving the desired power with a smaller sample size. Although this design was appropriate for our diagnostic outcome, it does not allow for assessment by group of downstream outcomes, such as linkage to care. Another strength is the collection of real-world data on the screening approaches, which have been evaluated in villages and neighbourhoods in which they are to be used.

A limitation is that, in the initial trial phase, it became necessary to readjust CAD thresholds by site because the use of different x-ray equipment had a direct effect on the CAD score distribution. Consequently, the screening algorithms had to be reconstructed, which, for a few participants, led to missing outcomes based on the new test logic. However, a sensitivity analysis showed no effect of the threshold adjustments on the primary outcome. Another limitation concerns the inconsistent documentation relating to referrals of participants with presumptive but unconfirmed tuberculosis, which probably led to an overestimation of the number of people with clinical or radiological suspicion. Furthermore, our cost estimates were obtained in a trial context and were not optimised for large-scale programmatic implementation. Costs under routine conditions might differ owing to variations in infrastructure, staffing, supply chains, and operational efficiency. The economic component of this trial was limited to a within-trial cost analysis of the evaluated screening strategies. A more comprehensive model-based economic evaluation incorporating a broader set of comparators, including radiologist reading of chest

x-rays, would provide additional insights and could be explored in future research. Finally, downstream health-care costs were included only for participants with a confirmed tuberculosis diagnosis. However, as such costs would apply similarly across both screening approaches, our comparative analysis between the screening strategies remains robust.

In conclusion, community-based tuberculosis screening with the CAD4TBv7 approach identified more tuberculosis cases in the trial population, and was less expensive in terms of total cost and average cost per case of tuberculosis detected, than the CAD4TBv7-CRP approach. As shown in post-hoc analyses, the cost advantage of the CAD4TBv7 approach over the CAD4TBv7-CRP approach was maintained across all prevalence scenarios examined. Trace results on the Xpert Ultra tests contributed considerably to the detection of tuberculosis in the community, and warrant close follow-up and re-testing as part of future active case-finding campaigns. Our findings provide information on tuberculosis screening strategies for both national tuberculosis programmes and global health organisations.

Contributors

KR, BKMJ, AvH, NDL, BvG, TRG, LL, and IA conceived and designed the trial, with support from AV, FT, CB, JM, AKK, KM, TG, BK, AS, and SB. KR led the project. KR, AvH, JM, BvG, TZ, and LL acquired funding. RFG, RME, and AS managed the project. SB and IA were responsible for site coordination. AvH, SM, MKa, MKe, TM, TG, SB, and IA were responsible for trial conduct and collected the data. FV, BKMJ, and TRG conducted the statistical analysis; AV, HVH, and FT conducted the economic analysis; and KM and BvG oversaw the CAD analysis. JK was responsible for data management. KR, FV, HVH, BKMJ, and TD interpreted the data and wrote the initial draft of the manuscript. KR, FV, AV, HVH, BKMJ, AvH, SM, FT, CB, NDL, MKa, MKe, TM, JK, AKK, KM, BvG, TG, BK, RFG, RME, TZ, TD, TRG, LL, AS, SB, and IA reviewed the manuscript and approved the final version, had full access to all the data in the study, and had final responsibility for the decision to submit for publication. KR, FV, and HVH accessed and verified the underlying data.

Declaration of interests

TD received funding from Global Health EDCTP3 for the TASP and SAHRI projects. KR received funding from SNSF for a BRIDGE project. NDL received a travel grant for conference attendance from Gilead Sciences. All other authors declare no competing interests.

Data sharing

A pseudonymised dataset regarding the coprimary outcomes is hosted on a non-commercial data platform (https://doi.org/10.5281/zenodo.19068196) and will be made accessible, on the basis of scientific relevance of the intended use, by request to the corresponding author. The data will be shared for an unlimited period of time.

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