Use of point-of-care C-reactive protein testing for screening of tuberculosis in the community in high-burden settings: a prospective, cross-sectional study in Zambia and South Africa

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Summary

Background WHO recommends community-wide, systematic tuberculosis screening in high-prevalence settings. C-reactive protein has been proposed as a tuberculosis screening tool for people living with HIV. We aimed to assess the performance of a point-of-care C-reactive protein test for tuberculosis screening in the community in two countries with a high tuberculosis burden.

Methods We conducted a prospective, cross-sectional study in four communities in Zambia and South Africa, nested in a tuberculosis prevalence survey. We included adults (aged ≥15 years) who were sputum-eligible (tuberculosis-suggestive symptoms or computer-aided-detection score ≥40 on chest x-ray) and whose sputum was tested with Xpert Ultra and liquid culture. A 5% random sample of individuals who were non-sputum-eligible was also included. We calculated sensitivity and specificity of point-of-care C-reactive protein testing, alone and combined with symptom screening, to detect tuberculosis in participants who were sputum-eligible, compared with a microbiological reference standard (positive result in Xpert Ultra, culture, or both).

Findings Between Feb 19 and Aug 11, 2019, 9588 participants were enrolled in the tuberculosis prevalence study, 1588 of whom had C-reactive protein testing and received results (875 [55·1%] were women and girls, 713 [44·9%] were men and boys, 1317 [82·9%] were sputum-eligible, and 271 [17·1%] were non-sputum-eligible). Among participants who were sputum-eligible, we identified 76 individuals with tuberculosis, of whom 25 were living with HIV. Sensitivity of point-of-care C-reactive protein testing with a cutoff point of 5 mg/L or more was 50·0% (38/76, 95% CI 38·3–61·7) and specificity was 72·3% (890/1231, 69·7–74·8). Point-of-care C-reactive protein combined in parallel with symptom screening had higher sensitivity than symptom screening alone (60·5% [46/76, 95% CI 48·6–71·6] *vs* 34·2% [26/76, 23·7–46·0]). Specificity of point-of-care C-reactive protein combined in parallel with symptom screening was 51·7% (636/1231, 95% CI 48·8–54·5) versus 70·5% (868/1231, 67·9–73·0) with symptom screening alone. Similarly, in people living with HIV, sensitivity of point-of-care C-reactive protein combined with symptom screening was 72·0% (18/25, 95% CI 50·6–87·9) and that of symptom screening alone was 36·0% (9/25, 18·0–57·5). Specificity of point-of-care C-reactive protein testing combined in parallel with symptom screening in people living with HIV was 47·0% (118/251, 95% CI 40·7–53·4) versus 72·1% (181/251, 66·1–77·6) with symptom screening alone.

Interpretation Point-of-care C-reactive protein testing alone does not meet the 90% sensitivity stipulated by WHO's target product profile for desirable characteristics for screening tests for detecting tuberculosis. However, combined with symptom screening, it might improve identification of individuals with tuberculosis in communities with high prevalence, and might be particularly useful where other recommended tools, such as chest x-ray, might not be readily available.

Funding European and Developing Countries Clinical Trials Partnership.

Lancet Glob Health 2023; 11: e704–14

This online publication has been corrected. The corrected version first appeared at thelancet.com/lancetgh on May 15, 2023

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Introduction

Systematic community-wide screening for tuberculosis is recommended by WHO where population prevalence is 0·5% or higher[1] as a key strategy towards ending the tuberculosis epidemic by 2030, which is among the health targets of the UN Sustainable Development Goals.[2] The rationale behind systematic screening for tuberculosis is that it results in dual benefit: individuals might benefit from early diagnosis, improved treatment outcomes, and lower costs and financial losses associated with tuberculosis, while the community might benefit through reducing the population prevalence of tuberculosis and further transmission.[3,4]

Research in context

Evidence before this study

To identify previous evidence on the performance of C-reactive protein for screening of tuberculosis, we searched PubMed on Jan 23, 2023, with the terms "C-reactive protein" and "tuberculosis" and "screening" without restricting by language or date of publication. The studies we found were mostly done in people living with HIV. A 2017 meta-analysis on diagnostic accuracy of C-reactive protein found a high pooled sensitivity (93%, 95% CI 85–97) to detect pulmonary tuberculosis, with no differences by HIV status. We found only two studies conducted in people without HIV and three studies in mixed populations in countries with a high HIV–tuberculosis burden. All five studies were done in the context of passive case finding (inpatients or outpatients seeking health care, most of them presenting with symptoms suggestive of tuberculosis) and used a laboratory-based assay to measure C-reactive protein concentrations. Four studies measured C-reactive protein in stored plasma samples. Findings on C-reactive protein sensitivity were heterogeneous due to differences between studies in the study design and C-reactive protein concentration cutoffs and reference standards used. None of these studies assessed C-reactive protein in combination with symptom screening or with other screening tools for tuberculosis. We found no studies that prospectively assessed the performance of C-reactive protein using point-of-care tests, alone and in combination with symptom screening, in community settings in countries with a high tuberculosis burden. WHO has endorsed C-reactive protein as a new screening tool for tuberculosis in people living with HIV, guided by evidence from two systematic reviews and meta-analyses suggesting that C-reactive protein has similar sensitivity and higher or similar specificity to symptom screening for detecting tuberculosis in ambulatory individuals and inpatients. Specifically, C-reactive protein had a pooled sensitivity of 89% and specificity of 54% in ambulatory patients not on antiretroviral therapy and a pooled sensitivity of 98% and specificity of 12% in inpatients. In both groups, a combination of WHO-recommended four-symptom screening with C-reactive protein testing in parallel improved sensitivity compared with four-symptom screening alone. There is scarce evidence on the use of C-reactive protein outside clinical settings and in populations not limited to people living with HIV. WHO has, consequently, highlighted the need for studies to evaluate the accuracy of C-reactive protein when used as a stand-alone test and when combined with other screening tools in other populations and across different epidemiological settings.

Added value of this study

To our knowledge, this is the first prospective study to assess the performance of point-of-care C-reactive protein testing, alone and in combination with symptom screening, for identifying tuberculosis in the community in countries with a high disease burden. Furthermore, this is the largest of all the studies assessing the performance of point-of-care C-reactive protein for detecting tuberculosis. Community-based screening is inherently more challenging than facility-based screening. In the community, tuberculosis prevalence is usually lower and earlier stage disease (paucibacillary) is more common, making tuberculosis detection harder. However, we conducted this study within a tuberculosis prevalence survey, using rigorous methodology, such that risk of bias selecting participants was carefully addressed and the reference standard used was robust. We found that in Zambia and South Africa, point-of-care C-reactive protein (using a cutoff of 5 mg/L) in those with symptoms suggestive of tuberculosis or with an abnormal chest x-ray was far from meeting the minimum sensitivity (90%) stipulated by WHO's target product profile for desirable characteristics for screening tests for detecting tuberculosis. However, point-of-care C-reactive protein testing in this context had a higher sensitivity than that of symptom screening, and the combination of C-reactive protein and symptom screening resulted in a higher sensitivity than that of any of these screening tools alone for detecting tuberculosis.

Implications of all the available evidence

Previously published data supported the use of C-reactive protein testing to systematically screen for tuberculosis in people living with HIV. Our study adds evidence on the use of C-reactive protein using a point-of-care test, which, alone and combined with symptom screening, might improve identification of people with tuberculosis in the community in countries with a high tuberculosis prevalence, where laboratory-based assays or other recommended tools, such as chest x-ray, might be of low availability and challenging to scale up.

To facilitate scale-up of systematic screening for tuberculosis, WHO has specified an urgent need to identify new rapid, simple, and low-cost practical screening tools that efficiently distinguish people with a high probability of having tuberculosis from those who are unlikely to have tuberculosis, reducing the proportion of individuals who would require costly confirmatory testing.

In the 2021 WHO Consolidated Guidelines on Tuberculosis, tools recommended for screening in the general population in countries with a high tuberculosis burden, alone or in combination, are symptom screening for clinical features associated with pulmonary tuberculosis, chest x-ray, and WHO-recommended molecular rapid tests.[5] Symptom-based tuberculosis screening is by far the most feasible, easy to implement, and low-cost of all screening tools. However, it has been shown to have low sensitivity and it is subjective depending on the interpretation of the provider conducting the screen and the person being screened.[5] Chest x-ray is one of the most accurate tools to detect tuberculosis, although it can be expensive and logistically challenging to use outside health facilities.[6] Molecular rapid tests improve the accuracy of symptom screening in populations at high risk of tuberculosis but

have substantial resource implications that might limit their use in some settings.[5,7]

C-reactive protein is a non-specific, acute-phase inflammatory biomarker detected in plasma. Concentrations of C-reactive protein have been shown to increase with infections, including tuberculosis,[8] and it is now available as a simple, low-cost, and rapid point-of-care assay that can be done on blood from fingerprick. C-reactive protein testing has been added for the first time to the 2021 WHO guidelines as a new screening tool for tuberculosis in people living with HIV in settings with a high tuberculosis burden. Point-of-care C-reactive protein has been shown to have a similar sensitivity and higher or similar specificity to symptom screening in this particular context, but evidence is scarce for its performance in the general population outside clinical settings.[8–14] WHO has highlighted the need to evaluate the accuracy of C-reactive protein when used as a stand-alone test but also when combined with other screening tools across different populations.[5]

In this study, we investigated the clinical performance of point-of-care C-reactive protein, alone and combined with other screening tools, for detecting active tuberculosis in the community in two countries with a high tuberculosis and HIV burden.

Methods

Study design

This was a prospective, cross-sectional study done in adults participating in a tuberculosis prevalence survey in 21 communities in Zambia and South Africa.

The tuberculosis prevalence survey was part of the Tuberculosis Reduction through Expanded Antiretroviral Treatment and Screening for Active Tuberculosis (TREATS; NCT03739736) project. TREATS aimed to assess the effect of the PopART trial intervention (population-level screening for tuberculosis combined with universal testing and treatment for HIV in the community) on tuberculosis outcomes (prevalence, incidence of infection, and notification rates).[15]

The TREATS tuberculosis prevalence survey consisted of two phases, one intensive diagnostic phase in four communities and one non-intensive diagnostic phase in the remaining 17 communities. The intensive diagnostic phase aimed to improve the understanding of the discordance between the Xpert Ultra assay and liquid culture in a tuberculosis prevalence survey and to design the tuberculosis diagnostic algorithm that was implemented in the non-intensive diagnostic phase.

This was a substudy embedded in the TREATS tuberculosis prevalence survey in the intensive diagnostic phase in three communities in Zambia, located in the Lusaka district (Lusaka Province), and one community in South Africa, located in the Cape Metro district (Western Cape Province). All four communities have a high HIV prevalence, ranging from 15% to 19% in 2019.[15]

The outcomes of this substudy were not part of the TREATS primary objectives; therefore, this substudy was not considered in the TREATS design. However, data collection were planned before both the point-of-care C-reactive protein tests and the reference tests were performed.

This study was approved by the London School of Hygiene & Tropical Medicine Ethics Committee (reference 14905), by the University of Zambia Biomedical Research Ethics Committee (reference 005–02–18) and National Health Research Authority in Zambia, and by the Pharma-Ethics Independent Research Ethics Committee in South Africa (reference 180219727).

Participants

Households were randomly selected for inclusion in the TREATS tuberculosis prevalence survey. Within each community, random sampling was structured according to geographically defined blocks of around 200 households. For every randomly selected block, all households were visited by a research assistant. If an adult household member was found at home, permission was sought to enumerate (list) all household members. In enumerated households, an individual was eligible to participate in the tuberculosis prevalence survey if they were a community resident aged 15 years or older. Eligible individuals were given barcoded invitation cards and invited to attend a mobile field site for further investigations. Written informed consent was obtained from all participants in this study.

Procedures

The procedures conducted at the mobile field sites are described in detail elsewhere.[16] Centrally in each census zone, a mobile field site was set up where the OneStopTB Platform (Delft Imaging, Hertogenbosch, Netherlands)—a truck containing a digital x-ray and Xpert Ultra (Cepheid, Sunnyvale, CA, USA) instrument—was stationed together with a set of tents where different survey procedures were performed. All eligible participants attending the mobile field site were administered a questionnaire on sociodemographic characteristics (including self-reported sex and age), were screened for symptoms suggestive of tuberculosis, and had a digital chest x-ray.

The chest x-rays were read and scored using computer-aided-detection software (CAD4TB version 5.0, Delft Imaging) that provided an output score between 0 and 100 related to the likelihood of the participant having tuberculosis. The tuberculosis symptom screen was defined as positive if participants reported either a cough lasting 2 weeks or longer, or two or more symptoms suggestive of tuberculosis (fever, chest pain, night sweats lasting ≥2 weeks, or unexpected weight loss over ≥1 month).

Individuals who were positive on the symptom screening or had a computer-aided-detection score of 40 or more, or who did not undergo chest x-ray, were

considered eligible for sputum examination. Participants who were sputum-eligible were asked to provide two on-the-spot sputum samples taken 1 h apart, which were tested in the OneStopTB platform using Xpert Ultra according to the manufacturer's instructions on the same day. All individuals who were sputum-eligible were requested to return to the mobile field site the following day to receive the Xpert Ultra results and for clinical management. All individuals reporting back on day 2 were also asked to provide a third on-the-spot sputum sample that was transported to a central laboratory for liquid culture testing using mycobacteria growth indicator tubes. Laboratory methods for Xpert Ultra and culture used in the TREATS tuberculosis prevalence survey in these communities are described in detail elsewhere.[16]

All participants were asked about HIV status. If an individual did not report being HIV-positive they were offered HIV testing using the national rapid diagnostic testing algorithm, whereby a first-line HIV serological antibody test (screening test) was performed and, if reactive, a second-line antibody test (confirmatory test) was conducted.[17] Counselling before and after being tested was provided by qualified and fully trained personnel following the national guidance on counselling and testing for HIV, allowing people to make informed decisions regarding knowledge of their HIV status and the implications of those decisions.

Participants who were diagnosed with HIV or tuberculosis, on the basis of at least one positive Xpert Ultra result or a positive culture, were referred for treatment initiation and linkage to care to the nearest health facility, following the country's national tuberculosis and HIV treatment guidelines. If participants had not returned for results and had microbiologically confirmed tuberculosis, they were traced by the study team and referred.

All the participants who were sputum-eligible as well as a random 5% sample (randomly selected by programming of the electronic data capture device) of those who were not sputum-eligible (negative on symptom screening and computer-aided-detection score <40) were asked to provide a fingerprick capillary blood sample for on-the-spot point-of-care C-reactive protein testing. 5% was chosen for the random sample based on a pragmatic approach but ensuring that differences between participants who were sputum-eligible and those who were non-sputum-eligible were captured with sufficient precision.

We used the Alere Afinion AS100 analyser (Abbott, Chicago, IL, USA) and C-reactive protein cartridge. This cartridge-based in-vitro rapid diagnostic test provides quantitative determination of C-reactive protein in 3–4 min and measurement range is 5–200 mg/L. Full information on the Alere Afinion C-reactive protein test procedure, quality control, and accuracy and precision data can be found in the manufacturer's instructions for use.[18]

We assessed several cutoff concentrations for C-reactive protein (5 mg/L, 8 mg/L, and 10 mg/L), above which we defined a C-reactive protein result to be positive. These thresholds are the most frequently used in population studies for tuberculosis.[5,8,19] For the evaluation of performance of point-of-care C-reactive protein within screening algorithms (figure 1), we used 5 mg/L as the cutoff, as this is recommended in the 2021 WHO guidelines for screening of tuberculosis in people living with HIV.

A microbiological reference standard was constructed, defined as tuberculosis-positive if either Xpert Ultra or

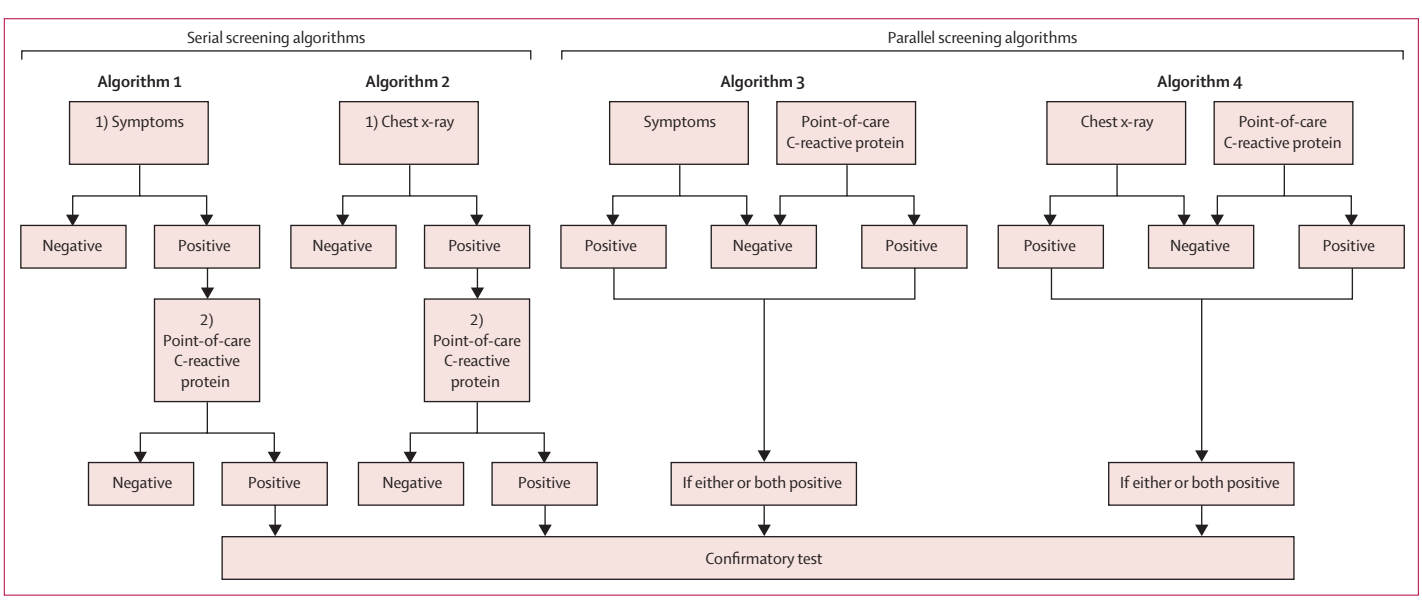

Figure 1: **Screening algorithms combining point-of-care C-reactive protein with symptom screening or chest x-ray**

culture final results were positive for *Mycobacterium tuberculosis* and defined as tuberculosis-negative if both Xpert Ultra and culture final results were negative. Xpert Ultra results were defined as negative if both sputum samples provided on the first day were "*M tuberculosis* not detected". Xpert Ultra results were defined as positive if either sample was graded as "*M tuberculosis* detected"—trace, very low, or above. The final culture result for each sample was defined on the basis of the combination of outcomes from the two Mycobacteria growth indicator tubes inoculated for each sample. The final culture result was classified as culture-positive if one or more tube result was positive for *M tuberculosis*. Those that were not culture-positive were classified as culture-negative if one or more tube results were negative for *M tuberculosis* or one or more tube results were positive for non-tuberculosis *Mycobacteria*, classified as contaminated if both tubes were contaminated, and classified as non-interpretable if both tubes were non-interpretable, or one was non-interpretable and one was contaminated. For this study, a valid culture result was one that was defined as culture-positive or culture-negative and from a batch where the positive control grew, and the negative control did not.

Staff reading the point-of-care C-reactive protein results were masked to results from the microbiological reference standard, and those assessing the test results confirming the microbiological reference standard results were masked to the point-of-care C-reactive protein results.

Statistical analysis

We chose to do this study in the four communities in the intensive diagnostic phase of the TREATS tuberculosis prevalence survey because they were the first sites to be included in the survey; however, no formal sample size calculation was conducted, as it was an opportunistic substudy that used all available data from the tuberculosis prevalence survey. However, given the sample of 10 000 participants in the four intensive-diagnostic-phase communities, and assuming that 15% of individuals would be sputum-eligible, of whom around 3–6% would be diagnosed with tuberculosis, a true sensitivity of point-of-care C-reactive protein of 70% to identify tuberculosis could be estimated with precision of around plus or minus 9–14%.

Baseline characteristics were collected for a random sample of 5% of participants who were non-sputum-eligible. The purpose of including individuals who were non-sputum-eligible was to describe C-reactive protein distribution in this general population, identify groups with higher and normal values, and use it as a comparator for the sputum-eligible group.

For descriptive statistics, dichotomous variables were reported as number (%) and continuous variables were reported as mean (SD). Comparisons between groups of categorical and continuous variables between sputum-eligible and non-sputum-eligible participants and between those with a point-of-care C-reactive protein less than 5 mg/L and those with a point-of-care C-reactive protein 5 mg/L or more were done using the Wilcoxon rank-sum test, *t* test, or χ^2 test as appropriate. A p value of less than or equal to 0·05 was considered significant.

The performance analyses of point-of-care C-reactive protein concentration and screening algorithms were conducted against the microbiological reference standard in participants who were sputum-eligible. Sputum-eligible participants had Xpert Ultra or culture performed as per the tuberculosis prevalence survey design; non-sputum-eligible participants did not have these tests. For the performance analysis, we calculated the point estimates and 95% CIs for the sensitivity, specificity, positive predictive value, negative predictive

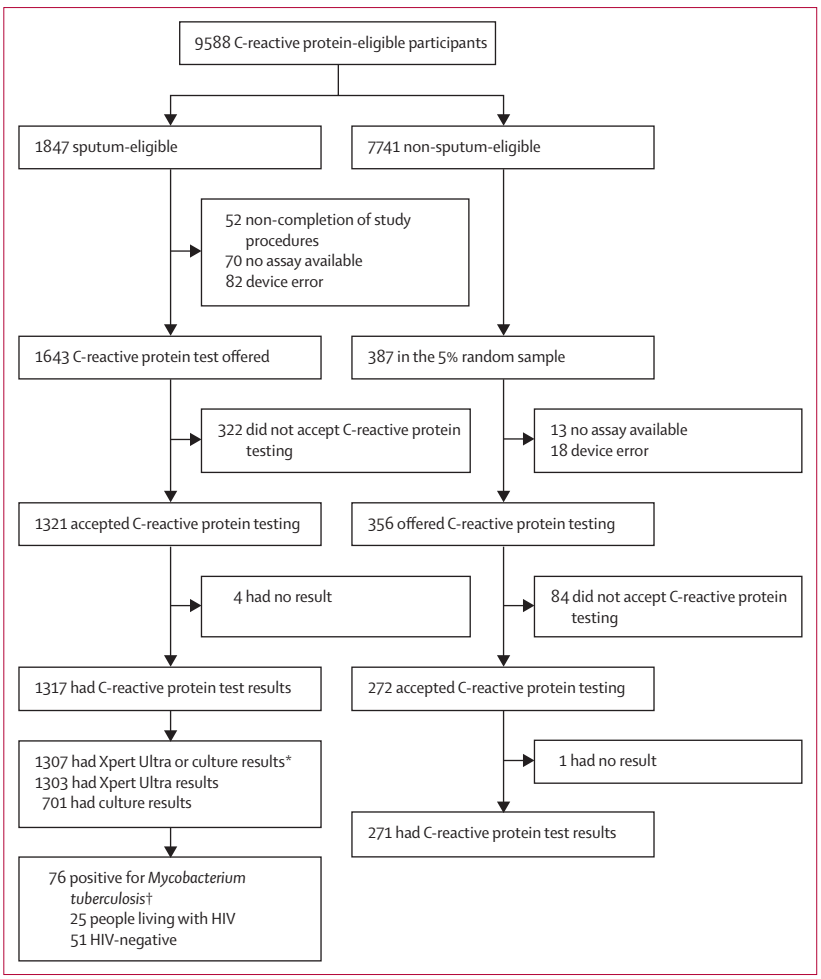

Figure 2: **Study flow chart**

*Four did not have Xpert Ultra results. 616 did not have culture results: 332 did not attend the mobile field site on the following day to submit sputum; 34 attended the mobile field site on the following day but did not submit sputum; 48 submitted sputum but results were excluded because positive control in the batch did not grow; 195 submitted sputum but results were contaminated; four submitted sputum but results were not interpretable; and one submitted sputum but results were missing. †30 were positive on Xpert Ultra and culture; 19 were positive on Xpert Ultra and negative on culture; seven were positive on culture and negative on Xpert Ultra; and 20 were positive on Xpert Ultra and had no culture results.

	All (n=1588)	Sputum-eligible* (n=1317)	Non-sputum-eligible† (n=271)	p value
Sex	..	..	..	<0·0001
Male	713 (44·9%)	621 (47·2%)	92 (33·9%)	..
Female	875 (55·1%)	696 (52·8%)	179 (66·1%)	..
Country	..	..	..	0·31
Zambia	1351 (85·1%)	1115 (84·7%)	236 (87·1%)	..
South Africa	237 (14·9%)	202 (15·3%)	35 (12·9%)	..
Age, years	..	..	..	<0·0001
15–24	370 (23·3%)	252 (19·1%)	118 (43·5%)	..
25–34	344 (21·7%)	269 (20·4%)	75 (27·7%)	..
35–44	334 (21·0%)	290 (22·0%)	44 (16·2%)	..
45–54	214 (13·5%)	193 (14·7%)	21 (7·7%)	..
≥55	326 (20·5%)	313 (23·8%)	13 (4·8%)	..
Previous tuberculosis‡	291 (18·3%)	282 (21·4%)	9 (3·3%)	<0·0001
Currently on tuberculosis treatment§	15 (0·9%)	15 (1·1%)	0	0·078
HIV status	..	..	..	0·0060
HIV-negative	1238 (78·0%)	1009 (76·6%)	229 (84·5%)	..
People living with HIV	318 (20·0%)	277 (21·0%)	41 (15·1%)	..
Unknown	32 (2·0%)	31 (2·4%)	1 (0·4%)	..
ART among people living with HIV	..	..	..	0·53
On ART	252 (79·2%)	218 (78·7%)	34 (12·5%)	..
Not on ART	66 (20·8%)	59 (21·3%)	7 (2·6%)	..
Point-of-care C-reactive protein concentration, mg/L	..	..	..	0·050
0–4·9	1144 (72·0%)	934 (70·9%)	210 (77·5%)	..
5·0–9·9	224 (14·1%)	185 (14·0%)	39 (14·4%)	..
10·0–14·9	82 (5·2%)	73 (5·5%)	9 (3·3%)	..
15·0–19·9	46 (2·9%)	42 (3·2%)	4 (1·5%)	..
≥20·0	92 (5·8%)	83 (6·3%)	9 (3·3%)	..
Mean C-reactive protein, mg/L	8·1 (15·9)	8·5 (16·9)	6·0 (9·5)	0·020

Data are n (%) or mean (SD). ART=antiretroviral therapy. *Sputum-eligible participants had tuberculosis symptoms, or a computer-aided-detection score ≥40 on chest x-ray, or no chest x-ray. †Non-sputum-eligible participants had no tuberculosis symptoms and a computer-aided-detection score <40. ‡Self-reported previous tuberculosis. §Self-reported to be currently on tuberculosis treatment.

Table 1: **Baseline characteristics of participants with a point-of-care C-reactive protein result by sputum eligibility status**

value, and area under the receiver operating characteristic curve for the diagnosis of tuberculosis. We evaluated the performance of different algorithms that combined symptom screening, point-of-care C-reactive protein testing, and chest x-ray sequentially or in parallel using a point-of-care C-reactive protein threshold of 5 mg/L. The computer-aided-detection score threshold above which we considered a chest x-ray to be positive was 40.

See Online for appendix

We also conducted exploratory analyses of the performance of point-of-care C-reactive protein and of the different screening algorithms compared with a microbiological reference standard considering an Xpert Ultra trace result as a negative tuberculosis result, and compared with only culture results and only Xpert Ultra results. We did performance analysis also by HIV status and in people living with HIV disaggregated by antiretroviral therapy (ART) initiation.

Participants with missing C-reactive protein results or missing or indeterminate Xpert Ultra and culture results were excluded from the analysis. We performed all analyses using STATA (version 17.0).

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

Between Feb 19 and Aug 11, 2019, 9588 participants were enrolled into the tuberculosis prevalence survey in the four communities in the intensive diagnostic phase. 1847 (19·3%) were sputum-eligible and qualified for point-of-care C-reactive protein testing and 387 (5·0%) of the remaining 7741 who were non-sputum-eligible were randomly sampled for point-of-care C-reactive protein testing (figure 2).

Of the 1847 participants who were sputum-eligible, point-of-care C-reactive protein testing was offered to 1643 (89·0%), 1321 (80·4%) of whom accepted and 1317 (80·2%) of whom had a C-reactive protein test result (figure 2). Reasons for participants not being offered a point-of-care C-reactive protein test included participants leaving the study site before completing procedures, device errors due, mostly, to high room temperature, and temporary unavailability of test cartridges (figure 2). Of the participants who were sputum-eligible with a C-reactive protein test result, 1303 (98·9%) had a final Xpert Ultra test result, and 701 (53·2%) had a valid culture result. Overall, 1307 (99·2%) participants had either an Xpert Ultra result or a valid culture result and were included in the analysis. Reasons for not having a culture result are shown in figure 2.

76 (5·8%) of 1307 participants were tuberculosis-positive according to the microbiological reference standard used (figure 2). 37 (48·7%) of 76 participants had a positive culture result and 69 (90·8%) had a positive result on Xpert Ultra, among whom 23 had trace *M tuberculosis*, 15 had very low *M tuberculosis*, 17 had low *M tuberculosis*, seven had medium *M tuberculosis*, and seven had high *M tuberculosis*.

Among participants who did not have a culture result, there was a higher proportion of women and girls, younger participants (age 15–24 years), participants with no previous tuberculosis, and participants from Zambia compared with participants who had a culture result (appendix p 1).

Among the 387 participants in the 5% random sample who were non-sputum-eligible, 356 (91·7%) were offered point-of-care C-reactive protein testing, of whom 272 (76·6%) accepted testing and 271 (76·3%) had a result (figure 2).

	Sputum-eligible* (n=1317)			Non-sputum-eligible† (n=271)		
	Point-of-care C-reactive protein <5 mg/L	Point-of-care C-reactive protein ≥5 mg/L	p value	Point-of-care C-reactive protein <5 mg/L	Point-of-care C-reactive protein ≥5 mg/L	p value
Sex	..	..	0·0030	..	..	0·60
Male	465 (74·9%)	156 (25·1%)	..	73 (79·3%)	19 (20·7%)	..
Female	469 (67·4%)	227 (32·6%)	..	137 (76·5%)	42 (23·5%)	..
Country	..	..	0·084	..	..	0·63
Zambia	801 (71·8%)	314 (28·2%)	..	184 (78·0%)	52 (22·0%)	..
South Africa	133 (65·8%)	69 (34·2%)	..	26 (74·3%)	9 (25·7%)	..
Age, years	..	..	0·0010	..	..	0·053
15–24	205 (81·3%)	47 (18·7%)	..	101 (85·6%)	17 (14·4%)	..
25–34	191 (71·0%)	78 (29·0%)	..	54 (72·0%)	21 (28·0%)	..
35–44	200 (69·0%)	90 (31·0%)	..	33 (75·0%)	11 (25·0%)	..
45–54	127 (65·8%)	66 (34·2%)	..	13 (61·9%)	8 (38·1%)	..
≥55	211 (67·4%)	102 (32·6%)	..	9 (69·2%)	4 (30·8%)	..
Previous tuberculosis‡	..	..	0·0070	..	..	0·41
Yes	182 (64·5%)	100 (35·5%)	..	8 (88·9%)	1 (11·1%)	..
No	742 (72·7%)	278 (27·3%)	..	202 (77·1%)	60 (22·9%)	..
Currently on tuberculosis treatment§	..	..	0·064	..	..	NA
Yes	10 (66·7%)	5 (33·3%)	..	0	0	..
No	1134 (72·1%)	439 (27·9%)	..	0	0	..
HIV status	..	..	<0·0001	..	..	0·14
HIV-negative	744 (73·7%)	265 (26·3%)	..	182 (79·5%)	47 (20·5%)	..
People living with HIV	169 (61·0%)	108 (39·0%)	..	27 (65·9%)	14 (34·1%)	..
Unknown	21 (67·7%)	10 (32·3%)	..	1 (100%)	0	..
ART among people living with HIV	..	..	1·0	..	..	0·73
On ART	133 (61·0%)	85 (39·0%)	..	22 (64·7%)	12 (35·3%)	..
Not on ART	36 (61·0%)	23 (39·0%)	..	5 (71·4%)	2 (28·6%)	..

ART=antiretroviral therapy. NA=not applicable. *Sputum-eligible participants had tuberculosis symptoms, or a computer-aided-detection score ≥40 on chest x-ray, or no chest x-ray. †Non-sputum-eligible participants had no tuberculosis symptoms and a computer-aided-detection score <40. ‡Self-reported previous tuberculosis. §Self-reported to be currently on tuberculosis treatment.

Table 2: **Characteristics of participants by sputum eligibility and point-of-care C-reactive protein concentrations**

Baseline characteristics of participants with point-of-care C-reactive protein results are shown in table 1. A higher proportion of participants who were sputum-eligible were male, in older age groups (age 35–44, 45–54, and ≥55 years), and were living with HIV compared with participants who were non-sputum-eligible (table 1). Participants who were sputum-eligible also had a higher mean C-reactive protein concentration than participants who were non-sputum-eligible (table 1).

In participants who were sputum-eligible, C-reactive protein concentrations of 5 mg/L or more were found more often in women, older participants (age 45–54 and ≥55 years), people living with HIV, and participants with previous tuberculosis (table 2).

Sensitivity and specificity of point-of-care C-reactive protein testing in participants who were sputum-eligible using a threshold of 5 mg/L or more against the microbiological reference standard are shown in table 3. Compared with the total sputum-eligible population with test results, in the subgroup of people living with HIV sensitivity of point-of-care C-reactive protein testing increased and specificity reduced (table 3). Increasing the C-reactive protein concentration threshold resulted in decreased sensitivity and increased specificity overall and in people living with HIV (table 3).

Sensitivity and specificity of different screening algorithms that include point-of-care C-reactive protein testing are shown in table 4. When point-of-care C-reactive protein testing was combined with other tests in a serial way (Algorithms 1 and 2), sensitivity was lower than that of any of the screening tools alone. However, when point-of-care C-reactive protein testing and symptom screening were conducted in parallel (Algorithm 3), the sensitivity was greater than when either symptom screening or point-of-care C-reactive protein testing were performed alone, although it was still lower than that of computer aided detection for chest x-ray alone (table 4). Conducting point-of-care C-reactive protein testing and computer aided detection for chest x-ray screening in parallel (Algorithm 4) did not increase sensitivity or specificity compared with computer aided detection for chest x-ray screening alone (table 4).

	n/N*	Sensitivity (95% CI)	n/N†	Specificity (95% CI)	n/N‡	Positive predictive value (95% CI)	n/N§	Negative predictive value (95% CI)	AUC (95% CI)
All participants									
Point-of-care C-reactive protein									
≥5 mg/L	38/76	50·0% (38·3–61·7)	890/1231	72·3% (69·7–74·8)	38/379	10·0% (7·2–13·5)	890/928	95·9% (94·4–97·1)	0·61 (0·55–0·67)
≥8 mg/L	28/76	36·8% (26·1–48·7)	1015/1231	82·5% (80·2–84·5)	28/244	11·5% (7·8–16·2)	1015/1063	95·5% (94·1–96·7)	0·60 (0·54–0·65)
≥10 mg/L	27/76	35·5% (24·9–47·3)	1062/1231	86·3% (84·2–88·1)	27/196	13·8% (9·3–19·4)	1062/1111	95·6% (94·2–96·7)	0·61 (0·55–0·66)
Symptoms¶	26/76	34·2% (23·7–46·0)	868/1231	70·5% (67·9–73·0)	26/389	6·7% (4·4–9·6)	868/918	94·6% (92·9–95·9)	0·52 (0·47–0·58)
Chest x-ray‖	73/76	96·1% (88·9–99·2)	260/1231	21·1% (18·9–22·5)	73/1044	7·0% (5·5–8·7)	260/263	98·9% (96·7–99·8)	0·59 (0·56–0·61)
People living with HIV									
Point-of-care C-reactive protein									
≥5 mg/L	15/25	60·0% (38·7–78·9)	158/251	62·9% (56·6–68·9)	15/108	13·9% (8·0–21·9)	158/168	94·0% (89·3–97·1)	0·61 (0·51–0·72)
≥8 mg/L	10/25	40·0% (21·1–61·3)	184/251	73·3% (67·4–78·7)	10/77	13·0% (6·4–22·6)	184/199	92·5% (87·9–95·7)	0·57 (0·46–0·67)
≥10 mg/L	10/25	40·0% (21·1–61·3)	197/251	78·5% (72·9–83·4)	10/64	15·6% (7·8–26·9)	197/212	92·9% (88·6–96·0)	0·59 (0·49–0·69)
Symptoms¶	9/25	36·0% (18·0–57·5)	181/251	72·1% (66·1–77·6)	9/79	11·4% (5·3–20·5)	181/197	91·9% (87·1–95·3)	0·54 (0·44–0·64)
Chest x-ray‖	24/25	96·0% (79·6–99·9)	48/251	19·1% (14·4–24·5)	24/227	10·6% (6·9–15·3)	48/49	98·0% (89·1–99·9)	0·58 (0·53–0·62)

AUC=area under the receiver operating characteristic curve. *n=those positive by C-reactive protein; N=those positive by composite reference standard. †n=those negative by C-reactive protein; N=those negative by composite reference standard. ‡n=true positive by C-reactive protein compared with composite reference standard; N=true positive by C-reactive protein plus false positive by C-reactive protein compared with composite reference standard. §n=true negative by C-reactive protein compared with composite reference standard; N=true negative by C-reactive protein plus false negative by C-reactive protein compared with composite reference standard. ¶Cough of 2 weeks or more or cough combined with two or more symptoms suggestive of tuberculosis (fever, chest pain, or night sweats for 2 weeks or more, or unexpected weight loss for at least 1 month). ‖CADTB4 score ≥40.

Table 3: **Performance of point-of-care C-reactive protein, symptom screening, and CAD4TB in chest x-ray in sputum-eligible participants for detecting tuberculosis compared with composite reference standard**

A similar pattern of results was found in people living with HIV (table 4). In this group, sensitivity of conducting point-of-care C-reactive protein testing and symptom screening in parallel was higher in those not on ART than in those who had initiated ART (appendix p 4).

Performance of point-of-care C-reactive protein and of the different screening algorithms against a microbiological reference standard considering Xpert Ultra trace results as tuberculosis negative, and against only Xpert Ultra and only culture results are in the appendix (pp 2–3).

Discussion

To our knowledge, this is the first study that evaluates the clinical performance of point-of-care C-reactive protein testing to identify people with tuberculosis in a community setting in countries with a high disease burden. In this study, point-of-care C-reactive protein testing, using a cutoff value of 5 mg/L or more, did not meet the minimum sensitivity (90%) stipulated by WHO's target product profile for desirable characteristics for screening tests for detecting tuberculosis.[20] However, point-of-care C-reactive protein testing detected more people with tuberculosis than symptom screening, and the combination of symptom screening and point-of-care C-reactive protein testing in parallel had higher sensitivity for tuberculosis detection than either of these screening tools alone.

Sensitivity of point-of-care C-reactive protein was 50·0%, which is lower than that found in previous studies assessing the performance of C-reactive protein for detecting tuberculosis.[19,21–23] Participants in our study were enrolled as part of a tuberculosis prevalence survey in the community, whereas previous studies were mostly conducted in clinical settings, with most studies being among people living with HIV.[19,23] In a community context such as ours, the population usually has fewer comorbidities and has a lower prevalence of tuberculosis and other infectious conditions compared with triage populations, with fewer individuals having higher C-reactive protein concentrations, resulting in a lower sensitivity and a higher specificity.[19,23]

We observed a higher sensitivity of point-of-care C-reactive protein testing in people living with HIV compared with overall sensitivity not disaggregated by HIV status. The few studies so far evaluating the performance of C-reactive protein in HIV-negative populations or in populations with mixed HIV status in countries with a high disease burden also found lower sensitivities than those performed exclusively in people living with HIV, although higher than that found in our study.[11,21,22,24–26] This higher sensitivity can be explained by the fact that previous studies were all conducted in either inpatients[11] or in symptomatic outpatients seeking health care[21,22,24–26] who are expected to be less well than our study population. Furthermore, four of the five studies performed C-reactive protein testing retrospectively in stored samples with laboratory-based assays, which might have implications for overall accuracy of C-reactive protein concentration.[26–28]

In the 2021 tuberculosis screening guidelines, WHO recommended C-reactive protein testing using a cutoff of more than 5 mg/L to screen for tuberculosis disease in people living with HIV, on the basis of evidence showing

	n/N*	Sensitivity (95% CI)	n/N†	Specificity (95% CI)	n/N‡	Positive predictive value (95% CI)	n/N§	Negative predictive value (95% CI)	AUC (95% CI)
All participants									
Serial screening algorithms									
Symptoms¶ then point-of-care C-reactive protein||	18/76	23·7% (14·7–34·8)	1122/1231	91·1% (89·4–92·7)	18/127	14·2% (8·6–21·5)	1122/1180	95·1% (93·7–96·2)	0·57 (0·53–0·62)
Chest x-ray** then point-of-care C-reactive protein||	38/76	50·0% (38·3–61·7)	959/1231	77·9% (75·5–80·2)	38/310	12·3% (8·8–16·4)	959/997	96·2% (94·8–97·3)	0·64 (0·58–0·70)
Parallel screening algorithms									
Symptoms¶ and point-of-care C-reactive protein||	46/76	60·5% (48·6–71·6)	636/1231	51·7% (48·8–54·5)	46/641	7·2% (5·3–9·5)	636/666	95·5% (93·6–96·9)	0·56 (0·50–0·62)
Point-of-care C-reactive protein† and chest x-ray**	73/76	96·1% (88·9–99·2)	191/1231	15·5% (13·5–17·7)	73/1113	6·6% (5·2–8·2)	191/194	98·5% (95·5–99·7)	0·56 (0·53–0·58)
People living with HIV									
Serial screening algorithms									
Symptoms¶ then point-of-care C-reactive protein||	6/25	24·0% (9·4–45·1)	221/251	88·0% (83·4–91·8)	6/36	16·7% (6·4–32·8)	221/240	92·1% (87·9–95·2)	0·56 (0·47–0·65)
Chest x-ray** then point-of-care C-reactive protein||	15/25	60·0% (38·7–78·9)	178/251	70·9% (64·9–76·5)	15/88	17·0% (9·90–26·6)	178/188	94·7% (90·4–97·4)	0·65 (0·55–0·76)
Parallel screening algorithms									
Symptoms¶ and point-of-care C-reactive protein||	18/25	72·0% (50·6–87·9)	118/251	47·0% (40·7–53·4)	18/151	11·9% (7·2–18·2)	118/125	94·4% (88·8–97·7)	0·60 (0·50–0·69)
Point-of-care C-reactive protein† and chest x-ray**	24/25	96·0% (79·6–99·9)	28/251	11·2% (7·5–15·7)	24/247	9·7% (6·3–14·1)	28/29	96·6% (82·2–99·9)	0·54 (0·49–0·58)

AUC=area under the receiver operating characteristic curve. *n=those positive by C-reactive protein; N=those positive by composite reference standard. †n=those negative by C-reactive protein; N=those negative by composite reference standard. ‡n=true positive by C-reactive protein compared with composite reference standard; N=true positive by C-reactive protein plus false positive by C-reactive protein compared with composite reference standard. §n=true negative by C-reactive protein compared with composite reference standard; N=true negative by C-reactive protein plus false negative by C-reactive protein compared with composite reference standard. ¶Cough of 2 weeks or more or cough combined with two or more symptoms suggestive of tuberculosis (fever, chest pain, or night sweats for 2 weeks or more or unexpected weight loss for at least 1 month). ||C-reactive protein concentration ≥5 mg/L. **CAD4TB score ≥40.

Table 4: **Performance of screening algorithms for detecting tuberculosis compared with composite reference standard in all participants and in people living with HIV**

that C-reactive protein offers a clinically significant improvement in accuracy over the WHO-recommended four-symptom screen, especially among outpatients starting ART. It has been suggested that sensitivity of C-reactive protein for detecting tuberculosis might be higher, and specificity lower, among people living with HIV with lower CD4 counts than among those with higher CD4 counts.[14] In this study, we did not capture CD4 counts among people living with HIV. However, overall, almost 80% of people living with HIV were on ART, which might explain why the sensitivity found was lower than that of previous studies in people living with HIV initiating ART.

The symptom screening definition used in this study was more restrictive than the WHO-recommended four-symptom screen, which could explain the lower sensitivity of our symptom screening.[29] We used prolonged cough or any two of the other symptoms from the TREATS tuberculosis prevalence survey because we knew from a previous study in Zambia and South Africa that this definition provides a more sensitive and specific screen than the WHO-recommended four-symptom screening.[29] However, we are aware of the limitations of symptom screening. Evidence is growing suggesting that individuals who do not report symptoms or do not have the classic tuberculosis symptoms form a large part of the reservoir of people with active tuberculosis.[30–33]

The systematic reviews and meta-analyses that guided the update of the WHO tuberculosis screening guidelines for systematic screening of people living with HIV compared sequential and parallel combination of C-reactive protein with the WHO-recommended four-symptom screen and, similar to what was found in this study, found that the parallel combination was more sensitive for detecting tuberculosis than the four-symptom screen alone.[34,35] Conversely, in the present study the combination of point-of-care C-reactive protein and computer aided detection for chest x-ray in parallel had no advantage in terms of sensitivity compared with computer aided detection for chest x-ray screening alone, although it reduced the number of people requiring confirmatory testing as a consequence of having a higher specificity.

The cost-effectiveness of the different algorithms is an important consideration that was not addressed in this study. Chest x-ray is more costly than symptom screening and point-of-care C-reactive protein, although digital chest x-ray has a low running cost, making it an attractive tool if the technology is already available. Point-of-care C-reactive protein costs between US$2 and $3 per test,

with results accessible in minutes and without the need for highly trained staff. Ultimately, cost-effectiveness also depends on the effect that different algorithms might have on transmission and on the interval in which they should be applied. Field studies comparing the cost-effectiveness of different algorithms and screening intervals are needed to better inform decision makers and screening models.

In our study, we used a robust microbiological reference standard. However, we included a large number of participants without a valid culture result in whom their tuberculosis outcome relied solely on Xpert Ultra. There is the possibility that we could have missed individuals who were culture positive and Xpert Ultra negative, thereby underestimating the overall number of people with tuberculosis and the sensitivity of C-reactive protein to detect them. However, there is evidence from the TREATS tuberculosis prevalence survey in these communities supporting that two Xpert Ultra results have a good sensitivity for detecting tuberculosis.[16]

The biggest limitation of this study is having conducted C-reactive protein performance analysis in a preselected population who either had symptoms or an abnormal chest x-ray. We acknowledge that there could have been individuals with tuberculosis among those who were asymptomatic and had a normal chest x-ray, and that by excluding them from the C-reactive protein performance analysis we might be limiting the translation of our findings to different populations.

Additionally, there were some participants who refused to get tested and C-reactive protein results could not be obtained for approximately 5% of participants, mostly because of challenges with the analyser, mainly due to the high ambient temperatures. Lateral flow tests are gradually evolving and could be thermally stable alternatives for measuring C-reactive protein in this context.

In summary, point-of-care C-reactive protein concentration has many desirable characteristics for tuberculosis screening in the community in countries with a high disease burden. Its use in parallel with symptom screening might have a role in future tuberculosis screening algorithms if the goals of screening are to maximise tuberculosis case detection or to measure the prevalence of tuberculosis in the population being screened, where computer aided detection for chest x-ray is not available. Further prospective studies assessing cost-effectiveness of different tuberculosis screening algorithms, including point-of-care C-reactive protein, across different populations are needed.

TREATS Study Team

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Contributors

MR contributed to the study design, contributed to implementation of the prevalence survey, conducted all analyses, led on conceptualising the paper, wrote the first draft of the paper, and is guarantor for the overall content of the paper. KS contributed to study design, provided oversight to all prevalence survey activities in Zambian communities, and contributed to revisions of the paper following the first draft. LM contributed to study design, provided oversight to all prevalence survey activities in South African communities, and contributed to revisions of the paper following the first draft. CW oversaw implementation of the prevalence survey in Zambian communities and contributed to revisions of the paper following the first draft. JMB oversaw implementation of the prevalence survey in South African communities and contributed to revisions of the paper following the first draft. BK and PdH contributed to study design, oversaw all laboratory work for the prevalence survey, contributed to implementation of the prevalence survey, contributed to conceptualising the paper, and contributed to revisions of the paper following the first draft. RH contributed to study design, to overall oversight of the TREATS study, to conceptualising the paper, and to revisions of the paper following the first draft. SFi contributed to study design, to overall oversight of the TREATS study, and contributed to revisions of the paper following the first draft. TG contributed to data management of the prevalence survey data, to conceptualising the paper, and to revisions of the paper following the first draft. AS contributed to data management for the prevalence survey, contributed to implementation of the prevalence survey, and contributed to revisions of the paper following the first draft. SFl contributed to study design, to conceptualising the paper, and to revisions of the paper following the first draft. EK oversaw implementation of the TREATS tuberculosis prevalence survey across all study communities, contributed to study design, contributed to conceptualising the paper, and contributed to revisions of the paper following the first draft. HA is the principal investigator of the TREATS study and provided overall oversight of the TREATS study, provided oversight of prevalence survey activities across Zambian and South African communities, took overall responsibility for study design, contributed to conceptualising the paper, and contributed to revisions of the paper following the first draft. SFl and EK have directly accessed and verified the underlying data reported in the manuscript. All authors read and approved the final version of the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

Datasets that enable others to reproduce the reported findings will be made openly available (publicly downloadable) immediately after publication. To protect the confidentiality of study participants, identifiable information will be excluded from all datasets that will be made available. These will be accompanied by documentation necessary to understand the content (such as data dictionaries or metadata descriptions). All source datasets will be made available through London School of Hygiene & Tropical Medicine Data Compass, subject to ethical, data protection, and other obligations being addressed. At the same time, they will be posted to the results section of the registry. Data will be publicly accessible and can be downloaded by anyone without restrictions.

Acknowledgments

This study was funded by the European and Developing Countries Clinical Trials Partnership, as part of the TREATS study with grant award number RIA2016S-1632. We express our appreciation and gratitude to all members of the TREATS study team in Zambia and South Africa for their hard work in sometimes difficult circumstances. We also appreciate the participation, time, and information sharing of the study participants and their communities. The content of this paper is solely the responsibility of the authors.

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