Screening for asymptomatic tuberculosis among adults with household exposure to pulmonary tuberculosis: a prospective observational cohort study

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Summary

Background More than half of tuberculosis cases detected by community prevalence surveys are classified as asymptomatic. We evaluated yield of symptom and chest radiograph screening of tuberculosis-exposed household contacts in South Africa.

Methods For this prospective observational cohort study, adult volunteers (aged ≥18 years) with household exposure within the past 6 months to patients with untreated or partially treated pulmonary tuberculosis, identified through local health services, were enrolled at three sites in South Africa (Worcester and Ravensmead, Western Cape Province, and Soweto, Gauteng Province). Household contacts were excluded if they were unlikely to attend study visits, or had conditions interfering with consent or study participation, including psychiatric illness, substance dependence, or incarceration. Systematic screening of tuberculosis symptoms (any duration), chest radiograph (any abnormality indicative of active tuberculosis), and sputum microscopy, Xpert Ultra, and liquid culture were performed. Serum C-reactive protein (CRP) was measured by multiplex bead array. Prevalent tuberculosis was microbiologically confirmed (Xpert Ultra or culture). Symptomatic and asymptomatic tuberculosis were defined as prevalent tuberculosis with and without reported symptoms compatible with tuberculosis. The primary outcome was the diagnostic yield (sensitivity) of microbiologically confirmed pulmonary tuberculosis.

Findings Between April 22, 2021 and Sept 22, 2022, 979 household contacts were enrolled, 345 (35·2%) male and 634 (64·8%) female, 185 (18·9%) living with HIV and 187 (19·1%) with previous tuberculosis. Prevalent tuberculosis occurred in 51 (5·2%) and was asymptomatic in 42 (82·4%) of 51. Only 13 (31·0%) of 42 asymptomatic people with tuberculosis were sputum-smear positive; eight (61·5%) of these 13 had a low bacillary burden, with smear grades scanty or 1+ (1–99 acid-fast bacilli per 100 fields). CRP did not discriminate healthy household contacts from those with asymptomatic tuberculosis (area under the curve 0·60, 95% CI 0·47–0·73). An abnormal chest radiograph suggestive of tuberculosis was observed in 23 of 41 asymptomatic (sensitivity 56·1%, 95% CI 41·0–70·1) versus eight of nine symptomatic (sensitivity 88·9%, 56·5–98·0) people with tuberculosis. Sensitivity of chest radiograph in combination with symptom screening was 32 (64·0%) of 50 (50·1–75·9) for all prevalent tuberculosis.

Interpretation More than 80% of confirmed people with tuberculosis among household contacts were asymptomatic; chest radiograph screening missed more than 40% of these. Community prevalence surveys reliant on symptom-based and chest radiograph-based approaches might substantially underestimate the prevalence of asymptomatic tuberculosis in endemic countries.

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Introduction

Approximately 2·7 million (25%) of the estimated 10·8 million global people with tuberculosis went undiagnosed or untreated in 2023.[1] To decrease *Mycobacterium tuberculosis* transmission and reduce the global burden of disease, finding and treating these so-called missing millions is crucial. However, more than half of all tuberculosis found in community prevalence surveys has been classified as asymptomatic[2,3]—occurring in people who do not have, recognise, or report typical tuberculosis symptoms such as cough, fever, night sweats, and loss of weight.[4]

WHO has recognised the importance of asymptomatic (previously termed subclinical) tuberculosis for disease transmission and is currently reviewing its guidance to determine programmatic implications.[5] In mathematical

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Research in context

Evidence before this study

WHO guidelines for systematic tuberculosis screening recommend symptom screening and chest radiography, based on a Cochrane meta-analysis reporting 70·6% sensitivity (any tuberculosis symptom) and 94·7% sensitivity (any chest radiograph abnormality) for bacteriologically confirmed pulmonary tuberculosis. National tuberculosis prevalence surveys rely on a positive symptom screen or abnormal chest radiograph to trigger diagnostic sputum testing. This approach to community screening would, by definition, miss asymptomatic people with tuberculosis without chest radiograph evidence of disease. We reviewed the reference list of the aforementioned meta-analysis for active case-finding studies of adolescents and adults aged 15 years and older in community and contact-tracing settings. We did forward citation tracking and searched reference lists, including studies published in English between Jan 1, 1980, and Nov 1, 2024. We excluded studies that included children younger than 15 years, or that exclusively enrolled people with additional risk factors (HIV, diabetes, latent tuberculosis infection, or previous tuberculosis). We found 28 studies that had done universal sputum testing for bacteriologically confirmed pulmonary tuberculosis and reported 51·8% (95% CI 49·9–53·7; I^2 89·2%) pooled sensitivity for symptom screening (any symptom; 24 studies, 2969 people with tuberculosis) and 62·4% (59·3–65·3; I^2 88·3%) pooled sensitivity for chest radiograph (any abnormality; ten studies, 1123 people with tuberculosis). Only four studies (145 people with tuberculosis) reported accuracy of symptom screening in parallel with chest radiography (pooled sensitivity 67·3%, 57·3–75·9; I^2 87·1%), but these studies did not disaggregate symptomatic and asymptomatic disease. The substantial heterogeneity probably reflects underlying differences in study design and populations, diagnostic approaches, and variation in interpretation of index tests, and limits the reliability and generalisability of the pooled summary measures.

Added value of this study

We did systematic screening with universal sputum microbiological testing of 979 household contacts of people with pulmonary tuberculosis in three South African communities and compared tuberculosis symptom (any duration) and chest radiograph (any abnormality indicative of active tuberculosis) screening approaches against a microbiological reference standard. We detected confirmed pulmonary tuberculosis in 5·2% of household contacts, and 82·4% of these reported no symptoms. Asymptomatic tuberculosis in household contacts was paucibacillary and associated with low serum C-reactive protein concentrations that were indistinguishable from healthy controls, but distinct from symptomatic tuberculosis in a comparator group of clinic attendees. Sensitivity of chest radiograph screening for asymptomatic tuberculosis was only 56·1%; sensitivity of combined symptom and chest radiograph screening for all tuberculosis was marginally higher at 64·0%.

Implications of all the available evidence

Our findings from household contacts suggest that symptom-based and chest radiograph-based approaches are inadequate for community tuberculosis screening in South Africa and do not meet the WHO target product profile for a tuberculosis screening test (minimum 90% sensitivity, 70% specificity). National tuberculosis prevalence surveys that omit universal sputum microbiological testing might substantially underestimate the prevalence of asymptomatic tuberculosis in high-burden countries.

models, an estimated 50% of asymptomatic people with tuberculosis will never develop symptoms and recover, but left untreated, the other 50% remain infectious, and at risk of progression to symptomatic tuberculosis disease and death.[6] Despite purportedly being less infectious, epidemiological and modelling studies suggest that asymptomatic tuberculosis is responsible for a greater share of transmission than symptomatic disease, because of a longer duration of exposure before treatment.[7–9]

Finding and treating asymptomatic tuberculosis in the community is important, but, by definition, individuals with asymptomatic tuberculosis would not be detected by symptom-triggered surveillance. New tools are needed for community screening. Given that ascertainment of symptoms is subjective, health-seeking behaviour might be a more important determinant of diagnostic performance than simply the presence or absence of symptoms. Whether tools developed for triage of clinic attendees with symptomatic tuberculosis would perform similarly for community screening of asymptomatic tuberculosis, which is probably less severe, remains to be shown.

Most active case-finding studies, prevalence surveys, and public health programmes rely on symptom or chest radiographic screening,[2,3,10] to prioritise resources for diagnostic sputum testing. WHO guidelines[11] also recommend symptom and chest radiograph screening, based on a Cochrane meta-analysis reporting 70·6% sensitivity (any tuberculosis symptom) and 94·7% sensitivity (any chest radiograph abnormality) for bacteriologically confirmed pulmonary tuberculosis.[10] However, these data are primarily derived from national tuberculosis prevalence surveys, which rely on a positive symptom screen or abnormal chest radiograph to trigger diagnostic sputum testing, and would miss asymptomatic tuberculosis without chest radiograph evidence of disease.

Review of evidence before this study showed 51·8% (95% CI 49·9–53·7%; I^2 89·2%) pooled sensitivity for symptom screening (any symptom; 24 studies, 2969 people with tuberculosis) and 62·4% (59·3–65·3%; I^2 88·3%) pooled sensitivity for chest radiograph (any abnormality; ten studies, 1123 people with tuberculosis) in studies that performed universal sputum testing for

bacteriologically confirmed pulmonary tuberculosis (references in the appendix p 8). Only four studies (145 people with tuberculosis) reported accuracy of symptom screening in parallel with chest radiography (pooled sensitivity 67·3%; 57·3–75·9; I^2 87·1%), but these studies did not disaggregate symptomatic and asymptomatic disease (figure 1).

We aimed to understand the burden of asymptomatic tuberculosis disease among tuberculosis-exposed household contacts in communities in South Africa, and to evaluate the yield of systematic screening using universal sputum microbiological testing, symptomatology, and chest radiograph.

Methods

Study design and participants

In this prospective observational cohort study, the Regional Prospective Observational Research for Tuberculosis (RePORT) South Africa network enrolled participants at three sites in South Africa (Worcester and Ravensmead, Western Cape Province, and Soweto, Gauteng Province). All three study sites were located in districts with among the highest tuberculosis incidences in South Africa. Adult (age ≥18 years) index patients with microbiologically confirmed pulmonary tuberculosis were identified through local health services, and their adult household contacts were approached for participation with the consent of the index patient. The eligible household contact had household exposure to an index patient with untreated or partially treated pulmonary tuberculosis, defined as sleeping in the same household or at least 4 h of other close exposure to the index patient per week, within the past 6 months. Data on index tuberculosis patients were not systematically collected. Household contacts were excluded if they were unlikely to attend study visits, or had conditions interfering with consent or study participation, including psychiatric illness, substance dependence, or incarceration.

Symptom screening, chest radiograph, and spontaneously expectorated sputum collection for Xpert Ultra (Cepheid, CA, USA), liquid culture (Mycobacteria Growth Indicator Tube [MGIT], BACTEC, Beckton Dickinson, NJ, USA), and acid-fast microscopy were done at a baseline visit for all household contacts, regardless of symptoms. A participant was classified as symptomatic if they reported one or more of the following symptoms: cough, fever, weight loss, fatigue, night sweats, pleuritic chest pain, or haemoptysis, for any duration. Chest radiographs were read once by an investigator at each site using a standardised form and recorded as normal or abnormal (compatible with pulmonary tuberculosis), on the basis of absence or presence of any cavitation, opacity, mediastinal or hilar adenopathy, pleural effusion, bronchiectasis, or collapsed lung.

The microbiological reference standard (MRS) for microbiologically confirmed pulmonary tuberculosis disease was at least one sputum specimen positive by MGIT culture or Xpert Ultra (excluding trace positive results). Sputum induction was not done because it is not the current standard of care in South Africa. Participants who were unproductive of sputum, or with Xpert Ultra trace positive result only, were considered sputum negative in the primary analysis. Participants who, after investigation for tuberculosis at baseline, were not confirmed by positive sputum MGIT culture or Xpert Ultra, were defined as controls for the purpose of diagnostic analyses. The definition of prevalent tuberculosis was restricted to people diagnosed on sputum samples collected at the baseline visit. Symptomatic and asymptomatic tuberculosis was defined as microbiologically confirmed prevalent tuberculosis with or without reported symptoms of any duration. All participants diagnosed with tuberculosis disease were referred for treatment.

See Online for appendix

The study protocol was approved by the institutional research ethics committees at each participating South African site and at Vanderbilt University Medical Center, Nashville, TN, USA. All participants provided written, informed consent before participation.

Measurement of C-reactive protein (CRP)

CRP was measured in household contacts, and in a cohort of symptomatic clinic attendees recruited contemporaneously by the RePORT South Africa network (appendix p 4). This exploratory analysis aimed to understand interactions between symptomatology and health-seeking behaviour. CRP was measured using a multiplex bead array in cryopreserved serum samples to differentiate asymptomatic tuberculosis from asymptomatic controls among household contacts, and symptomatic tuberculosis from symptomatic controls among clinic attendees. Briefly, serum samples were collected at baseline, before tuberculosis diagnosis, and cryopreserved in 607 adults (aged ≥18 years) self-presenting to clinics with presumptive tuberculosis (199 sputum microbiologically confirmed symptomatic pulmonary tuberculosis, 408 symptomatic controls with negative sputum culture and Xpert Ultra) at five sites in South Africa. Samples were later thawed and assayed using multiplex bead array (Bio-Plex Pro Human Apolipoprotein 10-plex Assay Panel; BioRad Laboratories, CA, USA) on the Bio Plex platform (BioRad Laboratories) as previously described.[36]

Statistical analysis

The primary outcome was the diagnostic yield (sensitivity) of microbiologically confirmed pulmonary tuberculosis. Sample size was based on approximating WHO target product profile criteria with adequate precision. For diagnostic analyses of asymptomatic tuberculosis, we selected the minimum target product profile criteria for a triage test (sensitivity 90% and specificity 70%). With a minimum of 40 tuberculosis cases and 120 controls, if the true sensitivity were 90%, the 95% CI for the observed

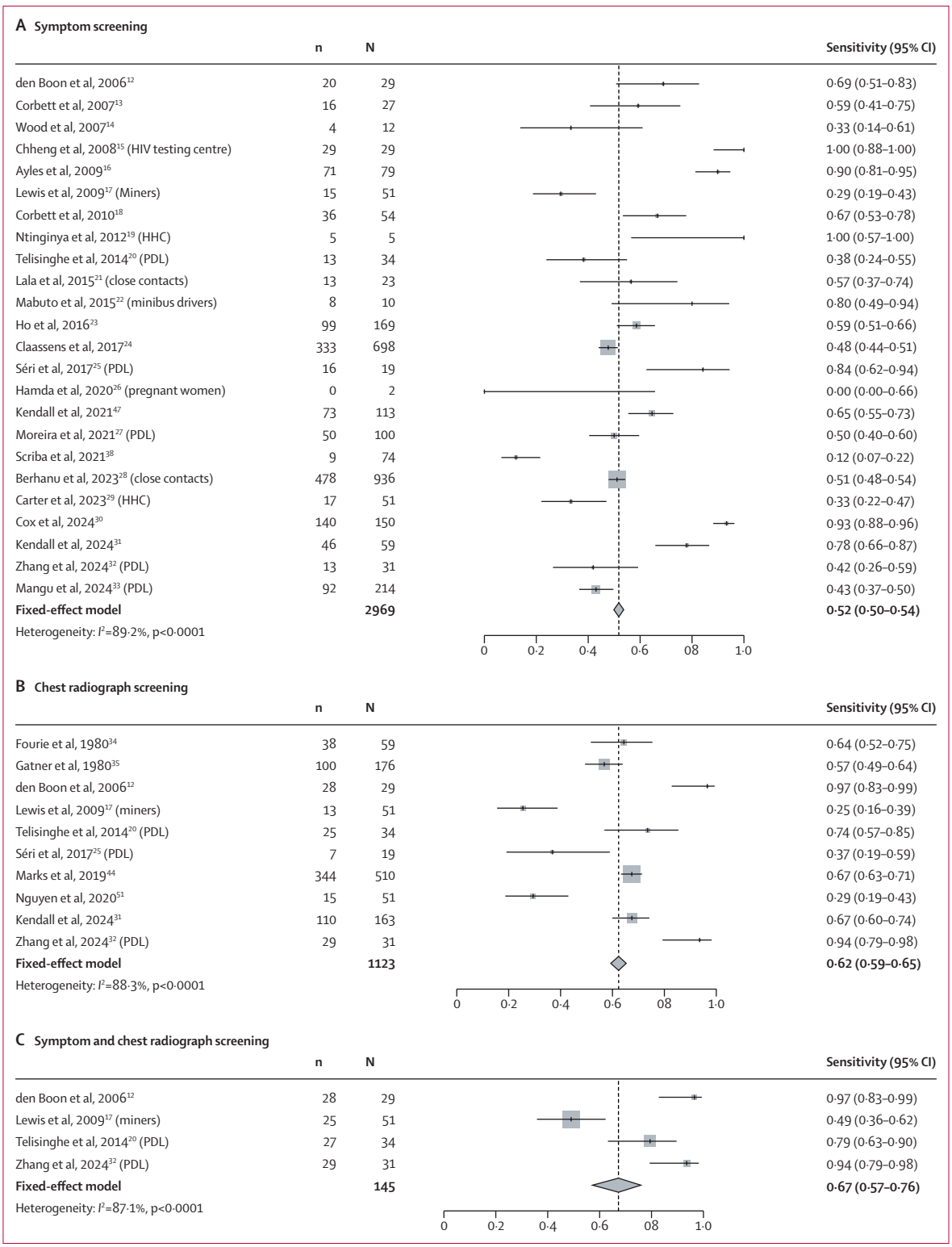

Figure 1: **Sensitivity of symptom and chest radiography screening for tuberculosis with universal sputum microbiological testing irrespective of presence of symptoms or chest radiograph abnormality**

Forest plot of the sensitivity of symptom screening (A), chest radiograph (B), and parallel symptom and chest radiograph screening (C) for tuberculosis reported in the literature. Cohorts are listed by year of publication and first author. HHC=household contacts. PDL=people deprived of liberty.

estimate would be 77–96%; conversely, if the true specificity were 70%, the 95% CI would be 61–78%. Analyses were done with Stata (version 16.1) and R (version 4.4.1). Sensitivity, specificity, and area under the curve (AUC) were calculated using standard methods. CIs for diagnostic accuracy measures were calculated with the Wilson method and DeLong method for AUCs. The number needed to test (NNT) with a confirmatory test to diagnose one person with tuberculosis was calculated as the number of confirmatory tests divided by the number of true positives with the screening approach. CRP concentrations were censored at 0·1 mg/dL (lower limit) and 150 mg/dL (upper limit).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, writing of this report, or decision to submit for publication.

Results

Between April 22, 2021, and Sept 22, 2022, 1001 household contacts were screened, and 979 enrolled (figure 2). The most common reasons for exclusion included insufficient exposure to an index patient with tuberculosis, active psychiatric condition, or alcohol or drug dependence, and other miscellaneous reasons (figure 2). Of 979 household contacts enrolled, 345 (35·2%) were male and 634 (64·8%) were female, median age was 34·8 years (IQR 25·4–48·2), 185 (18·9%) were living with HIV, 187 (19·1%) had known previous tuberculosis, and 834 (85·2%) were asymptomatic (table 1).

962 (98·3%) of 979 participants were able to provide a spontaneous expectorated sputum sample for testing. Prevalent, microbiologically confirmed, pulmonary tuberculosis disease was diagnosed in 51 (5·2%) of 979 participants: 30 (58·8%) by sputum Xpert Ultra and MGIT culture, 13 (25·5%) by sputum MGIT culture alone, and eight (15·7%) by sputum Xpert Ultra alone. Among those diagnosed by Xpert Ultra alone, five (62·5%) of eight had a previous tuberculosis episode, two of which occurred within the preceding 3 years (1·4 years and 1·8 years beforehand).

42 (82·4%) of 51 (95% CI 69·7–90·4%) people with prevalent tuberculosis did not report symptoms of any duration and were classified as asymptomatic. Among people with asymptomatic tuberculosis, 13 (31·0%) of 42 reported a previous tuberculosis episode, seven of which occurred within the preceding 3 years, and 32 (76·2%) of 42 were current or former smokers.

Chest radiograph was done in 41 (97·6%) of 42 people with asymptomatic tuberculosis, among whom abnormal chest radiographs indicative of tuberculosis were observed in 23 (56·1%) of 41 (95% CI 41·0–70·1); nine of 23 reported previous tuberculosis history. Conversely, abnormal chest radiographs were observed in eight (88·9%) of nine (56·5–98·0) people with symptomatic tuberculosis (difference in proportions 32·8%, 95% CI –2·5 to 50·4), and 106 (12·1%) of 879 (10·1–14·4) controls without tuberculosis. No chest radiograph abnormality was observed in 18 (43·9%) of 41 (29·9–59·0) asymptomatic tuberculosis cases.

Only 13 (31·0%) of 42 people with asymptomatic tuberculosis were sputum-smear microscopy positive. Among these, eight (61·5%) of 13 had a low bacillary burden, with sputum-smear grades scanty or 1+ (1–99 acid-fast bacilli per 100 fields). Similarly, 15 (42·9%) of 35 people with Xpert Ultra-positive asymptomatic tuberculosis were in the trace (not included in MRS) and very low semiquantitative categories, with eight (22·9%) additional cases graded as low, four (11·4%) graded as medium, and eight (22·9%) graded high. Median time to culture positivity for people with asymptomatic tuberculosis was 14 days (IQR 7–17).

People with symptomatic tuberculosis had higher rate of sputum smear microscopy positivity and greater sputum acid-fast bacillary burden, a higher rate of Xpert Ultra positivity, with fewer graded semiquantitatively as trace or very low, and shorter MGIT culture time to positivity. However, there were few people with symptomatic tuberculosis and therefore differences compared with asymptomatic tuberculosis were not formally tested.

Seven (16·7%) of 42 people with asymptomatic tuberculosis were diagnosed by Xpert Ultra alone (MGIT culture negative), only two of whom had a previous

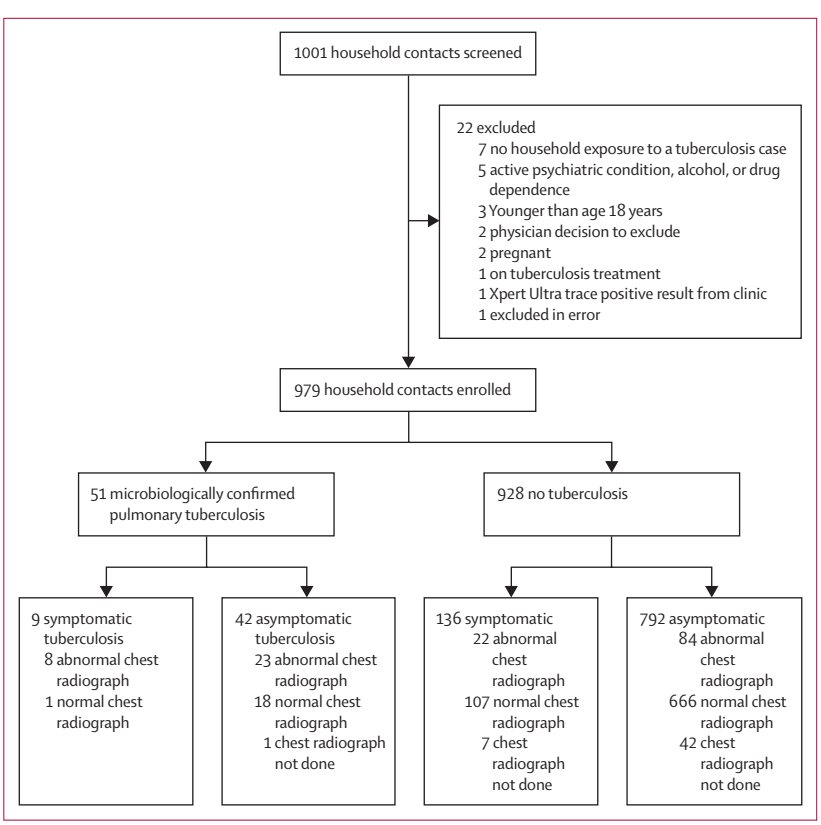

Figure 2: **Study flow diagram**

	Total (n=979)	Asymptomatic household contacts with tuberculosis (n=42)	Symptomatic household contacts with tuberculosis (n=9)	Asymptomatic household contacts without tuberculosis (n=792)	Symptomatic household contacts without tuberculosis (n=136)
Median (IQR) age	34·8 (25·4–48·2)	35·8 (25·8–49·3)	40·3 (31·7–49·6)	33·3 (24·7–45·8)	43·4 (32·0–53·8)
Sex					
Female	634 (64·8%)	21 (50·0%)	5 (55·6%)	523 (66·0%)	85 (62·5%)
Male	345 (35·2%)	21 (50·0%)	4 (44·4%)	269 (34·0%)	51 (37·5%)
Ancestry					
Black African	463 (47·3%)	6 (14·3%)	3 (33·3%)	349 (44·1%)	105 (77·2%)
Mixed ancestry	512 (52·3%)	36 (85·7%)	6 (66·7%)	439 (55·4%)	31 (22·8%)
Caucasian	4 (0·4%)	0	0	4 (0·5%)	0
History of smoking					
Never	410 (41·9%)	10 (23·8%)	1 (11·1%)	340 (42·9%)	59 (43·4%)
Current smoker	515 (52·6%)	30 (71·4%)	6 (66·7%)	414 (52·3%)	65 (47·8%)
Former smoker	54 (5·5%)	2 (4·8%)	2 (22·2%)	38 (4·8%)	12 (8·8%)
History of drug use	129 (13·2%)	11 (26·2%)	3 (33·3%)	98 (12·4%)	17 (12·5%)
Prior tuberculosis	187 (19·1%)	13 (31·0%)	4 (44·4%)	134 (16·9%)	36 (26·5%)
HIV positive	185 (18·9%)	7 (16·7%)	2 (22·2%)	129 (16·3%)	47 (34·6%)
Chest radiography					
No abnormality suggestive of tuberculosis	792/929 (85·3%)	18/41 (43·9%)	1/9 (11·1%)	666/750 (88·8%)	107/129 (82·9%)
Any abnormality suggestive of tuberculosis	137/929 (14·7%)	23/41 (56·1%)	8/9 (88·9%)	84/750 (11·2%)	22/129 (17·1%)
Not done	50	1	0	42	7
Median (IQR) persons in household	6 (4–8)	6 (4–9)	6 (3–8)	6 (4–8)	5 (4–7)
Study site					
Ravensmead	167 (17·1%)	6 (14·3%)	0 (0%)	160 (20·2%)	1 (0·7%)
Worcester	447 (45·7%)	29 (69·0%)	6 (66·7%)	382 (48·2%)	30 (22·1%)
Soweto	365 (37·3%)	7 (16·7%)	3 (33·3%)	250 (31·6%)	105 (77·2%)
Tuberculosis symptoms	145 (14·8%)	0	9 (100%)	0	136 (100%)
Chest pain	35 (3·6%)	0	4 (44·4%)	0	31 (22·8%)
Cough	104 (10·6%)	0	8 (88·9%)	0	96 (70·6%)
Fever	36 (3·7%)	0	1 (11·1%)	0	35 (25·7%)
Fatigue	24 (2·5%)	0	5 (55·6%)	0	19 (14·0%)
Loss of weight	57 (5·8%)	0	6 (66·7%)	0	51 (37·5%)
Night sweats	39 (4·0%)	0	6 (66·7%)	0	33 (24·3%)
Microbiological confirmation*					
Smear positive	24 (2·5%)	13 (31·0%)	4 (44·4%)	5 (0·6%)*	2 (1·5%)*
Scanty or 1+	15 (1·5%)	8 (19·0%)	1 (11·1%)	4 (0·5%)*	2 (1·5%)*
2+	7 (0·7%)	4 (9·5%)	2 (22·2%)	1 (0·1%)*	..
3+	2 (0·2%)	1 (2·4%)	1 (11·1%)	..	..
Culture positive	43 (4·4%)	35 (83·3%)	8 (88·9%)	..	..
Median (IQR) time to culture positivity (days)	14 (7–18)	14 (7–17)	12 (9–18)	..	..
Xpert Ultra positive	47 (4·8%)	35 (83·3%)	9 (100%)	3 (0·4%)*	0
Trace*	9 (0·9%)	5 (11·9%)	1 (11·1%)	3 (0·4%)*	0
Very low	12 (1·2%)	10 (23·8%)	2 (22·2%)	..	..
Low	10 (1·0%)	8 (19·0%)	2 (22·2%)	..	..
Medium	6 (0·6%)	4 (9·5%)	2 (22·2%)	..	..
High	10 (1·0%)	8 (19·0%)	2 (22·2%)	..	..

Data are n (%) unless otherwise stated. *Reference standard for the analysis is positive sputum culture or Xpert Ultra, excluding trace positive.

Table 1: **Characteristics of the study population by tuberculosis phenotype**

tuberculosis episode within the previous 3 years (1·4 years and 1·8 years). There were also three asymptomatic household contacts with negative MGIT culture and trace positive Xpert Ultra results (not included in the MRS); two of three had a previous tuberculosis episode within the preceding 3 years.

15 (83·3%) of the 18 people with asymptomatic tuberculosis without chest radiograph abnormality

suggestive of tuberculosis were sputum MGIT culture positive, with longer median MGIT culture time to positivity of 16 days (IQR 10–19), very low Xpert Ultra semiquantitative *M tuberculosis* load, and 11 (73·3%) of 15 were smear negative. The three participants with negative MGIT culture all had very low semiquantitative Xpert Ultra results and negative sputum smears; two of three had previous tuberculosis episodes, both more than 3 years before.

Universal sputum microbiological testing detected 18 people with asymptomatic tuberculosis (35·3%, 95% CI 23·6–49·0) that would have been missed by symptom-triggered and chest radiograph-triggered investigation for tuberculosis (figure 3), increasing yield by 54·5% (95% CI 38·0–70·2).

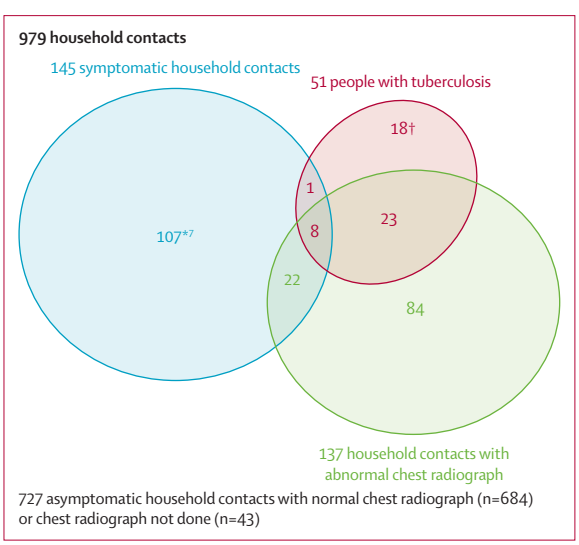

Figure 3: **Venn diagram demonstrating yield of symptom screening and chest radiography for detection of pulmonary tuberculosis among household contacts**

*Seven symptomatic household contacts without tuberculosis who did not have a chest radiograph. †One asymptomatic household contact with tuberculosis who did not have a chest radiograph.

Universal testing of household contacts with both sputum Xpert Ultra and MGIT culture (MRS) required 19·2 (95% CI 14·7–25·1) confirmatory tests to diagnose one case of tuberculosis. We explored the incremental yield (sensitivity) and number of confirmatory tests needed to diagnose one tuberculosis case for different screening strategies (table 2). A symptom screening approach with sensitivity 17·6% (9·6–30·3) would have missed 42 (82·4%) of 51 people with tuberculosis (69·7–90·4). Chest radiograph screening with sensitivity 62·0% (48·2–74·1) would have missed 19 (38·0%) of 50 (25·9–51·8) of all tuberculosis cases, but reduced the number of confirmatory tests needed to diagnose one tuberculosis case to 7·7 (95% CI 5·6–10·6) with, or 4·4 (3·3–6·1) without, parallel symptom screening. The addition of symptom screening in parallel to chest radiograph screening marginally increased sensitivity to 64·0% (50·1–75·9). However, among asymptomatic household contacts, chest radiograph screening with sensitivity 56·1% (41·0–70·1) would have missed 18 (43·9%) of 41 (29·9–59·0) of people with asymptomatic tuberculosis.

CRP was measured in a subset of 25 asymptomatic and seven people with symptomatic pulmonary tuberculosis and 126 healthy household contacts from this cohort: and 607 symptomatic adults presenting to clinic with tuberculosis symptoms (199 people with symptomatic pulmonary tuberculosis and 408 symptomatic controls without tuberculosis). CRP concentrations appeared higher among symptomatic tuberculosis cases (median 17·8 mg/dL, IQR 8·1–29·4) presenting for health care than in people with symptomatic tuberculosis detected among household contacts (median 4·3 mg/dL, IQR 1·7–11·0; figure 4).

CRP was able to differentiate symptomatic clinic attendees with and without symptomatic tuberculosis (AUC 0·84, 95% CI 0·81–0·88), and household contacts with and without symptomatic tuberculosis (AUC 0·74, 0·52–0·96), but was not able to discriminate between household contacts with asymptomatic tuberculosis

	Number of participants included in the analysis	Number of positive screening tests	Tuberculosis cases diagnosed		NNT with confirmatory tests to diagnose one case (95% CI)
			Number	Sensitivity (95% CI)	
No screening; MRS for all*	979	979 (100·0%)	51/51	100·0% (93·0–100)	19·2 (14·7–25·1)
Sputum Xpert Ultra for all†	979	47 (4·8%)	36/43	83·7% (70·0–91·9)	1·3 (1·2–1·6)
Symptom screening*‡	979	145 (14·8%)	9/51	17·6% (9·6–30·3)	16·1 (8·8–30·3)
Chest radiograph screening*§	929‖	137 (14·7%)	31/50	62·0% (48·2–74·1)	4·4 (3·3–6·1)
Parallel symptom and chest radiograph screening*¶	929‖	245 (26·4%)	32/50	64·0% (50·1–75·9)	7·7 (5·6–10·6)
Chest radiograph screening among asymptomatic participants*	791**	107 (13·5%)	23/41	56·1% (41·0–70·1)	4·7 (3·3–6·8)

MRS=microbiological reference standard. NNT=number needed to test. *MRS is positive sputum culture or Xpert Ultra, excluding trace positive results. †MRS is positive sputum culture. ‡Any symptom of any duration. §Any chest radiography abnormality suggestive of tuberculosis. ¶Any symptom of any duration or any chest radiograph abnormality suggestive of tuberculosis. ‖50 participants without chest radiograph, including one asymptomatic tuberculosis case, were excluded. **43 asymptomatic participants without chest radiograph, including one asymptomatic tuberculosis case, were excluded.

Table 2: **Comparison of yield and NNT of different screening approaches for detection of tuberculosis cases among household contacts of index patients**

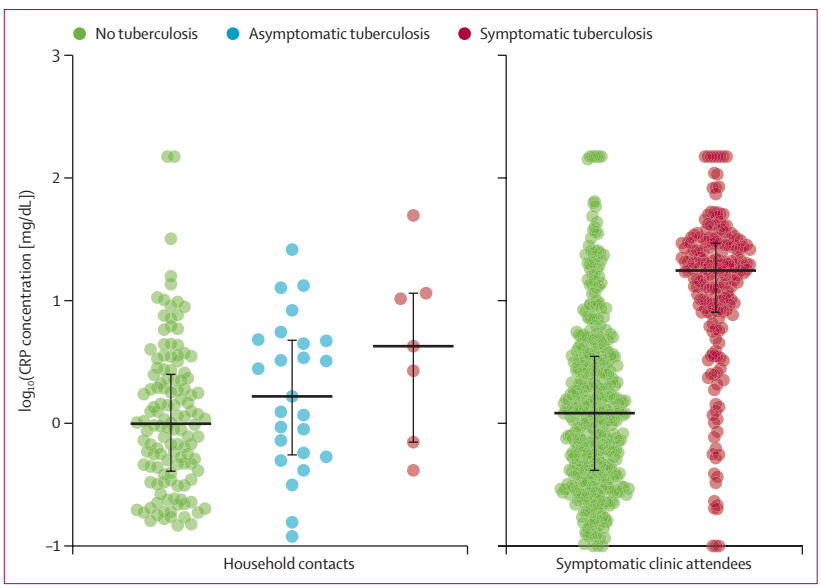

Figure 4: **CRP is unable to differentiate asymptomatic tuberculosis cases from household contacts without tuberculosis**

CRP concentration measured by multiplex bead array in a subset of 25 asymptomatic and seven symptomatic pulmonary tuberculosis cases, and 126 healthy household contacts, from this cohort, and 607 symptomatic adults presenting to clinic with tuberculosis symptoms (199 symptomatic pulmonary tuberculosis and 408 without tuberculosis). CRP concentrations were censored at 0·1 mg/dL (lower limit) and 150 mg/dL (upper limit) and are shown on a $\log_{10}$ scale. Each dot represents one participant. The midline is the median and the whiskers show IQR. CRP=C-reactive protein.

disease from those without tuberculosis (AUC 0·60, 0·47–0·73). Sensitivity of CRP for diagnosing asymptomatic tuberculosis among household contacts was 48·0% (30·0–66·5) when specificity was set at 70% per WHO target product profile minimum screening test criteria.[37] Conversely, with sensitivity set at 90%, specificity was 19·0% (13·1–26·8).

Discussion

We aimed to understand the burden and clinical characteristics of asymptomatic tuberculosis among tuberculosis-exposed household contacts in three communities in South Africa, and to measure the yield of universal symptom, chest radiograph, and sputum screening. We found 5·2% tuberculosis prevalence among household contacts in high-tuberculosis-burden districts, which is more than six times higher than the community rate reported in the South African national tuberculosis prevalence survey.[2] Reliance on symptom screening to trigger diagnostic tuberculosis investigation would have missed 82·4% people with microbiologically confirmed, asymptomatic tuberculosis in this cohort, in keeping with similar studies conducted in the community.[38] The yield of asymptomatic tuberculosis detected by active screening of all exposed household contacts, regardless of presence of symptoms, was 4·7 times that of symptomatic tuberculosis (nine [17·6%]). This ratio is consistent with modelling estimates of household *M tuberculosis* exposure and infection occurring within the preceding 6–12 months.[39]

The yield of chest radiograph screening for all tuberculosis alone or in combination with symptom screening was low. The observed sensitivity of chest radiograph screening for all tuberculosis among household contacts was considerably lower than the 94·7% expected by WHO but is consistent with the pooled 62·4% sensitivity derived from review of community-based screening studies (figure 1). It is also notable that 18 (43·9%) of 41 people with asymptomatic tuberculosis and normal chest radiographs not suggestive of active tuberculosis would have been missed by traditional screening methods. Stuck and colleagues[40] modelled the prevalence of asymptomatic pulmonary tuberculosis in adults in community settings and estimated even lower chest radiograph sensitivity of 25% among individuals with no cough.[40]

Given that sensitivity of screening approaches is independent of prevalence, the findings from this household contact study could be extrapolated to community prevalence surveys. The universal tuberculosis sputum screening methods used in this study detected 54·5% more tuberculosis than would a parallel symptom-triggered and chest radiograph-triggered approach, such as that adopted by the South African national tuberculosis prevalence survey.[2] Extrapolating our findings among household contacts in three high-tuberculosis-burden communities to the South Africa-wide community population survey, which observed a microbiologically confirmed pulmonary tuberculosis prevalence of 852 cases (95% CI 679–1026) per 100 000 population, the true prevalence of microbiologically confirmed tuberculosis, including chest radiograph-negative cases, might be as high as 1331 (1061–1603) per 100 000 population. If these findings from South Africa are replicated in other high-tuberculosis-burden countries in which national prevalence surveys omitted universal sputum microbiological testing of symptom-negative and chest radiograph-negative persons, it is probable that the global burden of asymptomatic tuberculosis has been substantially underestimated. The screening approach also has implications for tuberculosis control. The TREATS[41] and SCALE[42] community-based, cluster-randomised studies used symptom-based and chest radiograph-based active case finding, but failed to show effect on tuberculosis incidence compared with standard of care.[43] Conversely, the ACT3 study in Vietnam performed active, community-wide, universal sputum Xpert Ultra screening and demonstrated a reduction in incidence compared with standard of care, passive case detection.[43,44] Incomplete treatment of asymptomatic tuberculosis in the absence of universal sputum testing might explain this difference in outcome. Although our study did not include longitudinal follow-up of newly diagnosed tuberculosis to assess progression or treatment uptake, this remains a key priority for future research.

Our finding that symptom and chest radiograph screening, developed for triage of patients with

symptomatic tuberculosis seeking care, perform poorly as screening tests for asymptomatic tuberculosis in the community, is mirrored by our findings for CRP, which has been recommended by WHO as a tuberculosis screening tool for people living with HIV.[11] Studies have shown promising performance of CRP for tuberculosis triage among adults who are symptomatic attending outpatient clinics.[45,46] However, in our exploratory analysis, serum CRP concentrations were lower among people with tuberculosis among household contacts in the community compared with those in people with tuberculosis presenting to clinics, in keeping with the study by Kendall and colleagues.[47] Our findings also mirror those of Ruperez and colleagues;[48] CRP did not significantly differentiate asymptomatic tuberculosis from asymptomatic household contacts without tuberculosis, suggesting that CRP would not be appropriate as a screening test in a community setting. This finding is consistent with current WHO guidance, which does not recommend CRP for community screening in general populations without HIV.

People with asymptomatic tuberculosis also had predominantly paucibacillary sputum, with low Xpert Ultra semiquantitative and sputum-smear grade, and low CRP concentrations. Collectively, these data support the hypothesis that asymptomatic tuberculosis in the community, among people not presenting for health care, is associated with less severe disease and less systemic inflammation, than symptomatic tuberculosis diagnosed among clinic attendees. However, the potential contribution of asymptomatic tuberculosis to transmission should not be underestimated. Although individual bacillary burden might be low, the extended duration of undiagnosed tuberculosis disease in the household could permit sustained transmission over time because of cumulative exposure.[7–9] This finding also reinforces the principle that a triage test for symptomatic clinic attendees cannot be adopted uncritically as a community screening test among asymptomatic individuals. Performance of new screening tests for asymptomatic tuberculosis in the community should not be benchmarked against performance of those same tests for triage and diagnosis of symptomatic tuberculosis. Further, given the importance of mass community screening to detect asymptomatic tuberculosis, it has been proposed that tests with sensitivity lower than proposed in the WHO target product profile[13] might be acceptable.[49]

Although universal sputum testing demonstrated higher diagnostic yield in our study, we recognise that this approach is not practical for routine implementation at scale in most high-burden settings. Mass community chest radiograph screening in endemic settings could detect many people with undiagnosed tuberculosis if deployed at scale,[50] despite suboptimal sensitivity. However, control of the epidemic might require detection and treatment of a greater proportion of asymptomatic community tuberculosis, particularly the approximately 40% missed by chest radiograph screening in asymptomatic individuals. In the absence of more sensitive and scalable screening tools for asymptomatic tuberculosis, our findings support the use of universal sputum testing with either a molecular test or culture for selected high-risk groups, such as household contacts, in whom diagnostic yield is higher. Most surveys prescreen participants with symptom questionnaires and chest radiographs, which preferentially identifies individuals with more advanced or symptomatic disease and inflates the proportion of symptomatic tuberculosis among those tested. Although this approach might improve the apparent sensitivity of symptom and chest radiograph screening, it also risks underestimating the true burden of asymptomatic tuberculosis. Notably, Stuck and colleagues[40] reported a lower proportion of asymptomatic pulmonary tuberculosis in adults in community settings of 28% after adjustment. Our findings suggest that an additional 36% of asymptomatic tuberculosis could be identified through universal sputum testing, although this approach might not be affordable in many high-burden countries.

A particular strength of this study is the systematic approach to universal symptom, chest radiograph, and sputum screening. There were also several limitations. The under-representation of male participants in our study might reflect sex-related differences in participation or the characteristics of the index patients, introducing potential selection bias and limiting generalisability. Only spontaneously expectorated sputum samples were collected; it is possible that sputum induction or collection of multiple sputum samples might have yielded higher numbers of people with asymptomatic tuberculosis. We detected eight people with sputum MGIT culture-negative, Xpert Ultra-positive tuberculosis, five of whom had previous tuberculosis. However, only two of the previous episodes were within the preceding 3 years, which makes false positive Xpert Ultra results less probable. It is also possible that the chest radiograph reading methodology might have missed pathology. Chest radiographs were read once by an investigator at each site for any abnormality compatible with tuberculosis. This approach might have missed other subtle or non-specific findings, and might have resulted in lower sensitivity and higher specificity than an approach that targeted any abnormality. Although it is possible that additional readers might increase sensitivity, it is more probable that requiring concordance of two or more readers would improve specificity at the expense of sensitivity.[51] Specialised radiological training and expertise might further increase accuracy, but might not be readily available in tuberculosis-endemic settings. Chest radiograph reading with computer-assisted detection software meets or exceeds the minimum WHO target product profile for a tuberculosis triage test for symptomatic adults with presumptive tuberculosis,[37,46,52] and has been recommended by the WHO as an alternative to human readers. However, in the South African tuberculosis prevalence survey computer-assisted

detection accuracy was significantly lower in asymptomatic versus symptomatic individuals.[53] In future work, we plan to compare diagnostic accuracy of chest radiograph with several investigator readers to computer-assisted detection for diagnosis of asymptomatic tuberculosis. CRP concentrations were measured by multiplex bead array, rather than a validated, high-sensitivity assay platform. However, although assay sensitivity might differ, relative to symptomatic tuberculosis in clinic attendees, CRP concentrations appear to be lower in household contacts with asymptomatic or symptomatic tuberculosis. Our ability to assess CRP performance, particularly in asymptomatic individuals, was constrained by the small number of people with tuberculosis in this subgroup. Finally, tuberculosis symptoms were self-reported and subjective. Chronic or mild symptoms that did not interfere with daily function, such as a smoking-related cough, might have been perceived as normal. Perhaps more important than whether symptoms were truly present or absent, unlike a clinic triage scenario, all household contacts who participated in this study were not actively seeking health care.

Our study supports the idea that community screening approaches detect only a small proportion of people with tuberculosis,[54] given that symptom and chest radiograph screening missed approximately 40% of asymptomatic tuberculosis in this household contact-tracing study. If these findings in South Africa are replicated in other high-burden countries, in which national tuberculosis prevalence surveys have omitted definitive diagnostic testing of asymptomatic, chest radiograph-negative individuals, the global burden of asymptomatic tuberculosis could be substantially underestimated. Biomarkers developed and tested for triage of symptomatic tuberculosis, such as CRP, would also perform suboptimally as community screening tests for asymptomatic tuberculosis. These findings suggest that, pending discovery and validation of new non-sputum tuberculosis biomarkers for asymptomatic tuberculosis, accurate community-based tuberculosis screening requires universal sputum microbiological testing.

Contributors

TJS, TRS, and MH conceived the idea, raised funds, and provided the resources. GW, TJS, TRS, and MH wrote the study protocol and provided study oversight. MT, TM, STM, and FN were responsible for all site-level activities, including recruitment, clinical management, and data collection. KHa provided operational support and project management. NNC did the Luminex bead arrays. HM, AK, FM, RP, KHl, KS, and YFvdH cleaned and verified the underlying data. SCM, HM, and DTA analysed the data. SCM, HM, and MH interpreted the results and wrote the first draft. All authors had full access to the data, confirm the integrity of the data and its presentation, agree with its interpretation as discussed in the manuscript, and reviewed, revised, and approved the manuscript before submission. The corresponding author had final responsibility for the decision to submit for publication.

Declaration of interests

GW reports grant funding from the US National Institutes of Health, the Bill & Melinda Gates Foundation, and the European and Developing Countries Clinical Trials Partnership for tuberculosis-related research, travel support from the National Institute of Allergy and Infectious Diseases, and holds several patents related to tuberculosis diagnostics filed through Stellenbosch University. MH reports grant funding from the Civilian Research and Development Foundation (CRDF) Global and the South African Medical Research Council to the University of Cape Town for the Regional Prospective Observational Research for Tuberculosis (RePORT) South Africa project, as well as other clinical trial grants to the University. MH is a member of the WHO Technical Advisory Group for Tuberculosis Vaccines. TJS reports institutional grant support from CRDF Global, the US National Institutes of Health, and the South African Medical Research Council. TRS and YvdH report institutional grant support from CRDF Global for the RePORT South Africa project. All other authors declare no competing interests.

Data sharing

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available because of international data privacy regulations and ethical restrictions.

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