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Pulmonary Tuberculosis Infectiousness of Persons Identified Through Active and Passive Case-finding in a High-burden Setting

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Background. The role of active case-finding (ACF) in improving tuberculosis (TB) prevention and care depends on the infectiousness of persons with undiagnosed TB and the accuracy of screening strategies. To compare undiagnosed community dwellers to persons presenting for healthcare, we evaluated clinicodemographic and microbiologic characteristics, cough aerosol culture (CAC) status, and household contact (HHC) QuantiFERON-Plus (QFT) status by case-finding approach in adults with pulmonary TB.

Methods. We enrolled 388 Kenyan adults with GeneXpert (excluding trace) and/or culture-confirmed, untreated TB through healthcare presentation (passive case-finding [PCF]; 87%) or ACF (community-based prevalence survey). Interventions included cough aerosol sampling and HHC QFT testing. We performed mixed-effect logistic regression to predict transmission, clustered on index participants.

Results. World Health Organization–recommended screening symptoms (W4SS) were more common in the PCF cohort (99% vs 73%, $P < .001$). Traditional makers of infectiousness were less frequent in the ACF cohort. Higher symptom burden (number of reported World Health Organization-recommended 4-symptom screen) associated with higher bacillary burden (lower GeneXpert Ct) (estimate −0.55; 95% confidence interval [CI], −.98 to −.13; $P = .01$). Among 263 participants with CAC, 21% were CAC-positive, none of whom enrolled through ACF. Among 270 HHCs, QFT positivity differed by index CAC status (89% vs 56% in HHCs of CAC-positive and negative participants, respectively; $P < .001$) but not by traditional infectiousness makers or case-finding approach. Index CAC-positive status (adjusted odds ratio [aOR], 11.2; CI, 2.2–58.3), HIV-positive status (aOR, 0.1; CI, .0–.6), and HHCs age (aOR, 1.04; CI, 1.01–1.08), independently predicted HHC QFT positivity.

Conclusions. Our findings suggest that ACF may detect a smaller proportion of CAC-positive persons with TB than PCF.

Keywords. active case-finding; prevalent tuberculosis; subclinical tuberculosis; tuberculosis infectiousness; aerosol sampling.

In 2022, 7.5 million people were newly diagnosed with tuberculosis (TB), 3.1 million fewer than estimated from modeling and prevalence studies [1]. This gap is partially due to persons with TB in the community who do not pursue healthcare. Interest in active case-finding (ACF), systematic screening for TB rather than relying on healthcare seeking by symptomatic persons (ie, passive case-finding [PCF]), has grown in recent years [2]. However, evidence for the effectiveness of ACF in decreasing TB prevalence is mixed: 2 cluster-randomized trials that relied on participant symptoms for TB investigations [3, 4] showed no effect, whereas a study that screened for TB regardless of symptoms demonstrated a community-wide TB reduction [5]. Subclinical TB, defined as TB disease with detectable *Mycobacterium tuberculosis* (Mtb) but without clinically recognized symptoms [6], is common [7]: based on community surveys, 63% of persons with TB deny cough, whereas 28% deny any TB-related symptom [8]. These results suggest that persons with subclinical TB may contribute to community TB transmission. New strategies to identify these individuals are needed.

The importance of prioritizing ACF for TB prevention and care depends on the infectiousness of undiagnosed persons and the availability of cost-effective screening methods. Estimating TB infectiousness has traditionally relied on measures of bacillary burden, which correlate poorly with infectiousness [9–11]. Cough aerosol sampling system (CASS), a

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research tool that measures the cough aerosol culture (CAC) status of persons with TB, is the best-studied predictor of TB infectiousness [2]. Previous studies have evaluated characteristics of individuals with TB identified through ACF compared to PCF [12–14], and differences in symptom presentation have been demonstrated [8, 15, 16]. However, only 1 study evaluated the CAC status of persons identified through ACF [15], but did not include results from household contact (HHC) investigations.

To understand the estimated infectiousness of undiagnosed people with TB who are detected through ACF, the TB Aerobiology, Immunology, and Transmission study [17] compared the clinicodemographic and microbiologic characteristics of persons identified through ACF to PCF in Nairobi, Kenya, 1 of 30 high TB burden countries [1]. In a subgroup, we evaluated CAC status in index participants, the best validated estimator of infectiousness, and interferon-γ release assay (IGRA) results in HHCs as an indicator of transmission events. We hypothesized that CAC-positive persons would be identified through both PCF and ACF, with a lower frequency identified through ACF.

METHODS

Study Design

Study Setting and Participants. We enrolled adults ≥18 years with newly diagnosed pulmonary TB (PTB) and their HHCs in a prospective observational study in Nairobi, Kenya. Kenya is estimated to have a TB incidence of 348 per 100 000 population [18]. Nairobi County accounts for approximately 15% of persons with prevalent TB in Kenya [18]. We enrolled participants either through PCF or ACF.

PCF Cohort. Between 1 March 2021 and 31 October 2023, adults attending outpatient TB clinics were enrolled if they had a sputum sample that was GeneXpert positive, either MTB/RIF (Xpert MTB/RIF) or Ultra (Xpert Ultra, at a semiquantitative grade higher than trace positive) (Figure 1) [17]. GeneXpert is the initial recommended test for people suspected of TB in Kenya [19]. We collected spot and morning sputum samples for acid-fast bacilli (AFB) smear and culture.

ACF Cohort. Using methods similar to the 2015–16 National TB Prevalence Survey [18], we performed a community-based household survey in 9 previously surveyed Nairobi geographic clusters between 1 May and 30 November 2022. Individuals aged ≥15 years who had lived in the household for at least 30 consecutive days before the survey were eligible. Participants with a cough of any duration and/or chest X-ray (CXR) suggestive of TB were asked to provide spot and morning sputum specimens for AFB smear and culture; morning samples (spot if morning sample unavailable) also underwent Xpert Ultra testing. ACF participants with Xpert Ultra positive sputum (at a grade greater than trace positive) and/or Mtb culture-positive sputum were defined as the "ACF cohort with confirmed TB" and invited to enroll in additional study procedures, including CASS and prospective follow-up (Figure 1). These only included ACF participants aged 18 years and older.

Trace-positive Cohort. The cohort included prevalence survey participants (all ≥18 years) with only Xpert Ultra trace-positive/culture-negative sputum samples.

HHCs. From PCF and ACF cohorts with confirmed TB, we enrolled HHCs of any age who described their primary residence, based on sleeping 4 or more nights per week in that location, as the index case's household. HHCs must have resided there for ≥60 days prior to the index participant's TB diagnosis.

Ethical Approvals. This study was approved by the Kenya Medical Research Institute Scientific and Ethics Review Unit (048/3988) and the University of Washington institutional review board (STUDY00009209). All participants provided written informed consent.

Study Procedures

Participants With TB. We obtained clinical and demographic information using a standardized questionnaire. Infectious aerosols were collected using CASS. Other procedures included posteroanterior CXR and phlebotomy.

HHCs. A questionnaire was administered to HHCs to collect symptoms, demographics, and TB history. Age-appropriate symptom screening was conducted for children, including persistent cough, fever, night sweats, weight loss/poor weight gain, and lethargy/reduced playfulness. All participants underwent posteroanterior CXR (2-view if <10 years) and QuantiFERON-Plus (QFT) testing. HHCs with abnormal CXR and/or symptoms suggestive of TB submitted sputum (induced sputum or gastric aspirates for children ≤10 years as appropriate) for GeneXpert testing.

Laboratory Assays

All sputum samples were concentrated by centrifugation. AFB smears were examined using fluorescence microscopy. Sputum samples were decontaminated using the N-acetyl-l-cysteine-NaOH method, and pellets were inoculated in liquid media (MGIT, Becton-Dickinson, NJ) and incubated in a BACTEC MGIT 960 machine. Positive cultures were confirmed using Ziehl-Neelsen smear microscopy and MGIT TBc (Becton-Dickinson Diagnostic Instrument Systems, MD). GeneXpert testing was performed on raw sputum with results recorded as a cycle threshold (Ct) value, based on the lowest value of any of the rpoB probes and as a semiquantitative grade (negative, very low, low, medium, high, and "trace" added for Xpert Ultra) [20].

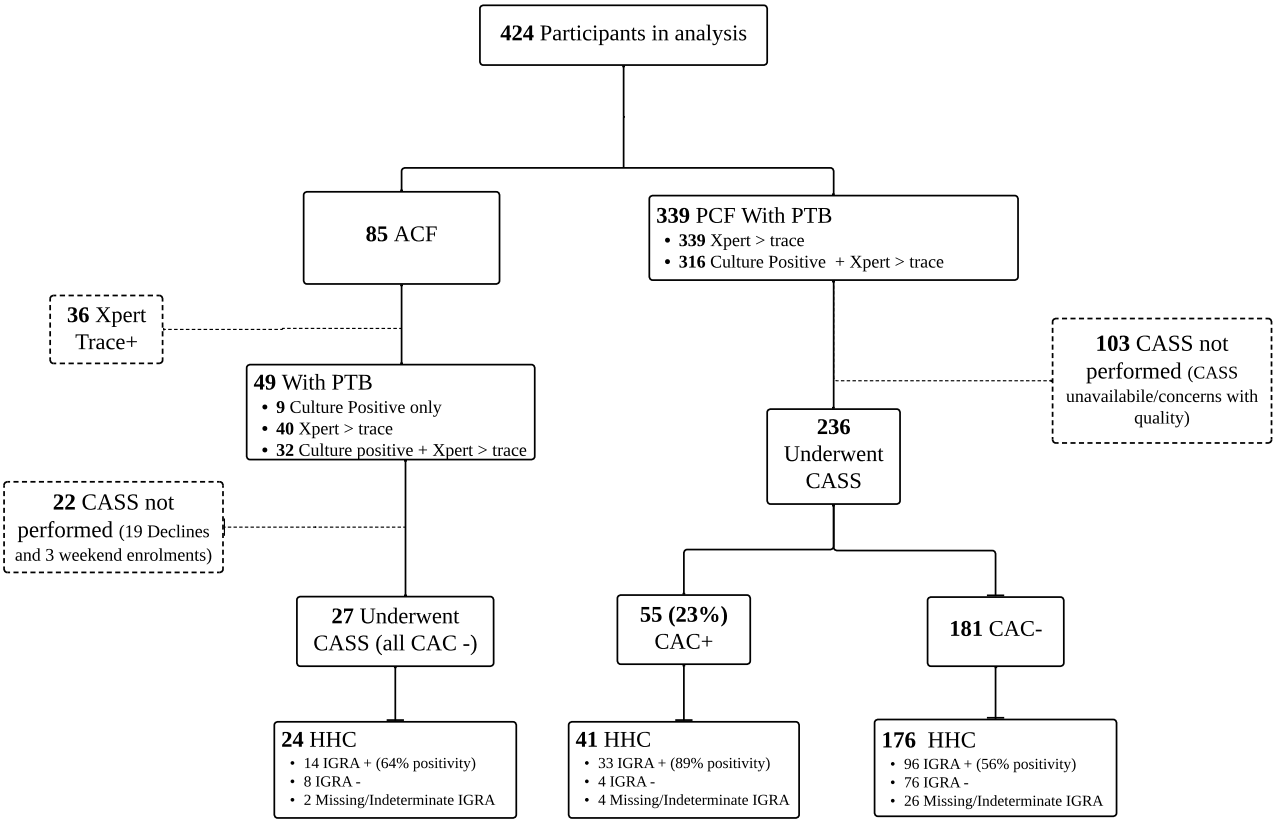

Figure 1. Enrollment and study flowchart. Among the 424 participants enrolled, 388 had confirmed tuberculosis (TB), 339 from clinics (passive case finding [PCF]), and 49 through a community-based prevalence survey (active case-finding [ACF]). Thirty-six individuals enrolled through ACF had an Xpert Ultra test that was trace-positive and sputum culture-negative and were excluded. Among the 339 participants with confirmed TB from clinics (PCF), 236 underwent the cough aerosol sampling system (CASS) procedure, of whom 55 had positive cough aerosol cultures, whereas among the 49 from ACF, 27 underwent the CASS procedure, all of whom had negative cough aerosol cultures. Quality concerns with the CASS procedure affected the PCF cohort since we began enrollment into the study with this cohort, and the initial period involved quality checks during setup. Participants in the ACF cohort who declined CASS were only willing to participate in the 1 time point prevalence survey in the community. A total of 241 household contacts (HHCs) residing with 97 index participants in whom CASS was performed were enrolled. The positivity rate is calculated after excluding indeterminate and missing results.

Participants with Xpert Ultra trace positive results (for whom rpoB probe Ct values were 0 were assigned a Ct value of 35.

CASS. As described previously, CASS (Thermo Fischer Scientific, IL) consists of a 6-stage Andersen Cascade Impactor, each stage holding a Middlebrook 7H10 or 7H11 solid agar plate on which aerosolized particles impact based on particle size [17, 21–23]. After collecting aerosols, plates were sealed and incubated at 37 °C for 8 weeks and observed weekly for growth. If growth was identified as Mtb, colony-forming units were counted. Participants were considered CAC-positive if at least 1 of the CASS plates had Mtb growth and CAC-negative if no CASS plates had Mtb growth and no more than 2 of 6 plates were contaminated with fungal or bacterial overgrowth [17].

An opt-out approach was used for HIV testing in persons with unknown status. CD4 lymphocyte count testing was performed in people with HIV at the time of inclusion. C-reactive protein (CRP) was measured (range, 0.6–350 mg/L) from serum (Cobas C 111, Roche Diagnostics, Switzerland). QFT testing and interpretation were conducted according to the manufacturer's protocol (Qiagen Diagnostics, Germany) [24]; indeterminate results were repeated, and we report the second result.

Statistical Analysis

We compared the characteristics of participants with TB by case-finding approach and CAC status using chi-squared or Wilcoxon rank-sum test. Using bivariate linear regression models, we evaluated associations between the total number of reported World Health Organization (WHO) TB screening symptoms (on a scale ranging from 0 to 4, with 1 point each for cough of any duration, fever, night sweats, and weight loss) and bacillary burden (assessed by GeneXpert Ct value), excluding trace-positive results. We evaluated index participant case-finding status, CAC status, and other measures of bacillary burden as determinants of QFT positivity in HHCs, stratified by HHC age. Based on past estimates of the background rate

of QFT positivity [17], we determined we would have 80% power to detect 72% and 40% QFT positivity in the HHC of PCF and ACF, respectively. We evaluated predictors of QFT positivity in HHCs using mixed-effect logistic regression models (*melogit* command in Stata) to account for clustering by index participant. The main predictor variable was CAC status, with other variables included as potential confounders and effect modifiers. The multivariable models included variables with P values $\leq .05$ in bivariate analyses. We used the forward selection stepwise regression method to develop multivariable models. Covariates were added sequentially, retaining only covariates that significantly improved model fit based on likelihood-ratio tests. Multicollinearity between independent variables was assessed using variance inflation factors.

Missing data were addressed by pairwise deletion in bivariate analysis, applying complete case analysis in assessing associations with CAC results and regression analyses. This was determined after evaluating the mechanisms of missing CAC data (*mcartest* command in Stata) and comparing characteristics of participants with missing and those with CAC results, concluding that the missingness was unsystematic. To test the robustness of our results, we assumed that the mechanism of missing results was "not at random" and performed worst-case scenario sensitivity analyses.

All statistical tests were two-sided with $\alpha = 0.05$. We performed analyses using Stata 17 (StataCorp, College Station, TX).

RESULTS

Baseline Characteristics and Healthcare-seeking Behavior

We enrolled 388 participants with confirmed TB, 339 through PCF, and 49 through ACF (Figure 1). The median age of participants was 34 years (interquartile range [IQR], 27–43). There were more women ($P = .02$) in the ACF compared to the PCF cohort (39%, 19/49) versus (23%, 79/339) (Table 1). WHO screening symptoms [25] were reported more commonly ($P < .001$) in the PCF cohort (99%, 336/339) compared to the ACF cohort (73%, 36/49). Cough of any duration was the most common symptom occurring in 89% (n = 378) of all participants (96% [325/339] versus 67% [33/49] in PCF and ACF cohorts, respectively, $P < .001$) (Table 1). Notably, participants in the PCF cohort had longer cough duration (8 [IQR 4–12] versus 4 [IQR 2–7] weeks, $P < .001$). Although weight loss was the second most common symptom among participants in the PCF cohort (87%, 293/338), among the ACF cohort, it was chest pain (47%, 23/49) (Table 1). In the PCF cohort, healthcare visits (for TB symptoms) preceding the enrollment visit occurred in 88% (299/339) of participants: 63% reported 1 visit, 19% 2 visits, and 18% 3 visits (Table 1). Most visits occurred at county hospitals or peripheral health facilities. In the ACF cohort, 27% (12/45) of participants reported a prior healthcare visit due to TB symptoms (Table 1).

Radiographic and Laboratory Evaluation

Compared to the ACF cohort, the PCF cohort had elevated inflammatory markers, including CRP (71.3 [IQR 34.4–106] versus 13.8 [IQR 2.6–33.4] mg/L, $P < .001$), and CXR findings of more advanced TB, including cavitations (68% [232/339] versus 37% [18/49], $P < .001$) and ≥1 quadrant affected by TB (98% [331/339] versus 85% [41/48], $P < .001$) (Table 1). The PCF cohort had markers of greater bacillary burden, including AFB-smear grade ($P < .001$), shorter time to detection of Mtb in liquid culture (5 [IQR 4–8] versus 13 [IQR 7–17] days, $P < .001$), lower GeneXpert Ct values (18.2 [IQR 16.5–22.2] versus 20.8 [IQR 17.6–26], $P < .001$), and 73% [245/336] versus 31% (15/49) had medium or high GeneXpert grades ($P < .001$). We evaluated associations between bacillary burden (GeneXpert Ct value) and the number of reported symptoms (scale 0–4) in 361 participants, including 321 and 40 in the PCF and ACF cohorts, respectively. A greater number of reported symptoms was associated with a lower GeneXpert Ct value (estimate −0.55; confidence interval [CI], −.98 to −.13; $P = .01$).

Trace Positive Cohort

We evaluated the characteristics of 36 participants identified through ACF with Xpert Ultra trace positive/culture-negative results (Table 1). Compared to those with confirmed TB, they were more likely to report prior TB (46% [6/13] versus 17% [63/367], $P = .008$) and no symptoms (36% [13/36] versus 4% [17/388], $P < .001$). Fewer had features of advanced TB based on CXR, bacillary burden, and inflammatory markers.

CAC Results

Next, we estimated TB infectiousness by assessing CAC status among participants with confirmed PTB. Reasons for not undergoing CASS included lack of CASS availability/concerns with quality (103 of 339 in the PCF cohort, 30%) and weekend enrollment through the prevalence survey (n = 3)/declining CASS enrollment (n = 19) (total 22 of 49 in the ACF cohort, 45%) (Figure 1). Participants who underwent CASS (236 PCF cohort, 27 ACF cohort) had similar sociodemographic characteristics as those who did not, but a higher proportion reported weight loss (84% [221/262] versus 75% [93/124], $P = .03$) and had significantly longer durations of cough (8 [IQR 4–14] versus 5 [IQR 3–8] weeks, $P = .003$), a higher proportion had positive AFB-smear (94% [243/260] versus 82% [102/124], $P \leq .001$) and Medium/High Xpert grade (71% [187/263] versus 60% [73/122], $P = .03$), and had lower CRP levels (62.1 [23.8–100.8] versus 79.8 [39.4–110.1] mg/dL, $P = .01$) (Supplementary Table 1). These associations remained when we compared participants who underwent CASS to those who did not when categorized by the case-finding approach. Among 236 PCF participants with CASS, 55 (23%) were CAC-positive; all 27 ACF cohort CASS participants were CAC-negative (Tables 1 and 2, Supplementary Table 2).

Table 1. Baseline Characteristics of Participants in the Passive Case-finding (PCF) and Active Case-finding (ACF) Cohorts

	PCF Confirmed TB N = 339	ACF Confirmed TB N = 49	PCF Versus ACF *P* value[a]	ACF Trace only N = 36	Total N = 424
Baseline characteristics					
Age, y (median, IQR)	34 [26.9–42.1]	35.7 [29–47.9]	.08	34 [26.5–44]	34.4 [27–43]
Women (n, %)	79 (23.3%)	19 (38.8%)	**.02**	17 (47.2%)	115 (27.1%)
Living with HIV (n, %)	45 (13.3%)	3/43 (7.0%)	.24	7 (19.4%)	55/418 (13.2%)
On ART (n, %)	23/44 (52.3%)	0/2 (0%)	.15	2/3 (66.7%)	25/49 (51.8%)
CD4 count, cells/mm^3, median [IQR]*	160 [53–284] n = 41	188.5 [92–285] n = 2	.84	591.5 [277–1060.5] N = 4	181 [62–306] n = 47
Previous history of TB (n, %)	59 (17.4%)	4/28 (14.3%)	.67	6/13 (46.2%)	69/380 (18.2%)
Tobacco use (current smoker) (n, %)	68 (20.1%)	11 (22.5%)	.67	4 (11.1%)	83 (19.6%)
Alcohol use (>0 drinks) (n, %)	156/338 (46.2%)	22 (44.9%)	.87	5 (13.9%)	183/423 (43.3%)
Heavy alcohol (≥5 drinks/day) (n, %)	39/156 (25.0%)	3/18 (16.7%)	.43	3/3 (100%)	42/177 (23.7%)
Symptoms and healthcare seeking					
Reported cough, any duration (n, %)	325 (95.9%)	33 (67.4%)	**<.001**	20 (55.6%)	378 (89.2%)
Cough ≥ 2 wk (n, %)	313/325 (96.3%)	26/33 (78.8%)	**<.001**	11/20 (55.0%)	350/378 (92.6%)
Cough duration, wk, median [IQR]*	8 [4–12]	4 [2–7]	**<.001**	2 [1–3.5]	6 [3–12]
Fever (n, %)	262 (77.3%)	12 (24.5%)	**<.001**	5 (13.9%)	279 (65.8%)
Weight loss (n, %)	293/338 (86.7%)	21/48 (43.8%)	**<.001**	8 (22.2%)	322/422 (76.3%)
Night sweats (n, %)	265 (78.2%)	21 (42.9%)	**<.001**	7 (19.4%)	293 (69.1%)
Number of W4SS symptoms[b] (n, %)					
0	4 (1.2%)	13 (26.5%)	**<.001**	13 (36.1%)	30 (7.1%)
1	12 (3.5%)	10 (20.4%)		14 (38.9%)	36 (8.5%)
2	43 (12.7%)	8 (16.3%)		4 (11.1%)	55 (13.0%)
3	74 (21.5%)	11 (22.5%)		2 (5.6%)	86 (20.3%)
4	207 (61.1%)	7 (14.3%)		3 (8.3%)	217/(51.2%)
Chest pain (n, %)	253 (74.6%)	23 (46.9%)	**<.001**	11 (30.6%)	287 (67.7%)
Previously sought healthcare for symptoms? (n, %)	299 (88.2%)	12/45 (26.7%)	**<.001**	5/34 (14.7%)	316/418 (75.6%)
One visit	188/299 (62.9%)	10/12 (83.3%)	**.35**	5/5 (100%)	203/316 (64.2%)
Two visits	56/299 (18.7%)	1/12 (8.3%)		0/5 (0%)	57/316 (18.0%)
Three visits	55/299 (18.4%)	1/12 (8.3%)		0/5 (0%)	56/316 (17.7%)
Place healthcare sought? (n, %)					
County hospital	91/299 (30.4%)	4/12 (33.3%)	.83	3/5 (60.0%)	98/316 (31.0%)
Peripheral facility	216/299 (72.2%)	5/12 (41.7%)	**.02**	2/5 (40.0%)	223/316 (70.6%)
Pharmacy	15/299 (5.0%)	1/12 (8.3%)	.61	0/5 (0%)	16/316 (5.0%)
Traditional healer	0/299 (0%)	0/12 (0%)	-	0/5 (0%)	0/316 (0%)
Private practitioner	22/299 (7.4%)	0/12 (0%)	.33	0/5 (0%)	22/316 (7.0%)
Other	2/299 (0.7%)	2/12 (16.7%)	**<.001**	0/5 (0%)	4/316 (1.3%)
Radiographic, microbiologic, and laboratory results					
CXR cavitary disease (n, %)	232 (68.4%)	18 (36.7%)	**<.001**	1/32 (3.1%)	255/419 (60.9%)
CXR quadrants (n, %)					
0	8 (2.4%)	7/48 (14.6%)	**<.001**	23/32 (71.9%)	38/419 (9.1%)
1	113 (33.3%)	17/48 (35.4%)		1/32 (3.1%)	131/419 (31.3%)
2	121 (35.7%)	7/48 (14.6%)		5/32 (15.6%)	133/419 (31.7%)
3	59 (17.4%)	3/48 (6.3%)		0/32 (0%)	62/419 (14.8%)
4	38 (11.2%)	14/48 (29.2%)		3/32 (9.4%)	55/419 (13.1%)
AFB-smear positive (n, %)	318/335 (94.9%)	27 (55.1%)	**<.001**	1 (2.8%)	346/420 (82.4%)
AFB-smear grade (n, %)					
Negative	17/335 (5.1%)	22 (44.9%)	**<.001**	35 (97.2%)	74/420 (17.6%)
Positive, scanty	27/335 (8.1%)	5 (10.2%)		0 (0%)	32/420 (7.6%)
Positive, 1+	75/335 (22.4%)	11 (22.5%)		1 (2.8%)	87/420 (20.7%)
Positive, 2+	74/335 (22.1%)	1 (2.0%)		0 (0%)	75/420 (17.9%)
Positive, 3+	142/335 (42.4%)	10 (20.4%)		0 (0%)	152/420 (36.2%)
Sputum culture (n, %)					
Negative	12/335 (3.6%)	9 (18.4%)	**.001**	32 (88.9%)	53/420 (12.6%)

Table 1. Continued

	PCF Confirmed TB N = 339	ACF Confirmed TB N = 49	PCF Versus ACF *P* value[a]	ACF Trace only N = 36	Total N = 424
Positive—Mtb	316/335 (94.3%)	39 (79.6%)		0 (0%)	355/420 (84.5%)
MOTT	2/335 (0.6%)	1 (2.0%)		0 (0%)	3/420 (0.7%)
Contaminated	5/335 (1.5%)	0 (0%)		4 (11.1%)	9/420 (2.1%)
Days to Mtb detection in MGIT, median [IQR]	5 [4–8] n = 316	13 [7–17] n = 39	**<.001**	-	6 [4–9] n = 355
Xpert grade (n, %)					
Negative	1/336 (0.3%)	5 (10.2%)	**<.001**	0 (0%)	6/421 (1.4%)
Trace	7/336 (2.1%)	4 (8.2%)		36 (100%)	47/421 (11.2%)
Very low	21/336 (6.3%)	9 (18.4%)		0 (0%)	30/421 (7.1%)
Low	62/336 (18.5%)	16 (32.7%)		0 (0%)	78/421 (18.5%)
Medium	106/336 (31.6%)	6 (12.2%)		0 (0%)	112/421 (26.6%)
High	139/336 (41.4%)	9 (18.4%)		0 (0%)	148/421 (35.2%)
Xpert Ct value, median [IQR]	18.2 [16.5–22.2] n = 328	20.8 [17.6–26] n = 44	**.01**	35**	19.1 [17.0–24.7] n = 408
CAC+ (n, %)	55/236 (23.3%)	0/27 (0%)	**.005**	-	55/263 (20.9%)
CRP, median [IQR]	71.3 [34.4–106] n = 336	13.8 [2.6–33.4] n = 26	**<.001**	0.99 [0.82–2.81] n = 13	66.6 [24.2–102.6] n = 375
WBC, median [IQR]	7.4 [6–9.3] n = 335	5.9 [4.8–7.3] n = 27	**.001**	5.6 [4.4–7.5] n = 12	7.3 [5.7–9.2] n = 374
Hgb, median [IQR]	13 [11.6–14.2] n = 335	13.7 [12.8–14.9] n = 27	**.02**	14.5 [13.2–15.2] n = 12	13.1 [11.7–14.4] n = 374
HbA1c, median [IQR]	5.8 [5.5–6.2] n = 334	5.3 [4.8–5.7] n = 27	**<.001**	5.1 [4.8–6.1] n = 13	5.8 [5.4–6.1] n = 374

Abbreviations: AFB, acid-fast bacilli; ART, antiretroviral therapy; CAC+, positive cough aerosol culture; CI, confidence interval; CRP, C-reactive protein; Ct, cycle threshold; CXR, chest X-ray; Hgb, hemoglobin; IQR, interquartile range; MOTT, Mycobacterium other than tuberculosis; Mtb, *Mycobacterium tuberculosis*; TB, tuberculosis; W4SS, World Health Organization-recommended 4-symptom screen; WBC, white blood cells. The bold values are factors meeting statistical significance at $P < .05$.

[a]*P* values are used to compare PCF and ACF cohorts with confirmed TB cohorts. The Wilcoxon rank-sum test was used to compare medians of continuous variables between the PCF and ACF groups, and chi-squared tests were used to compare proportions.

[b]Symptoms include cough, fever, night sweats, and weight loss.

*Limited CD4 counts available, PCF n = 39, ACF n = 2, trace n = 4, total n = 45.

**(Ultra Trace assigned 35).

Compared to CAC-negative participants in the PCF cohort, CAC-negative participants in the ACF cohort had shorter cough duration (4 vs 8 weeks, $P = .02$), a lower number of self-reported symptoms (3 vs 4, $P < .001$), fewer CXR quadrants affected by TB (1 vs 2, $P = .02$), lower measures of bacillary burden, including AFB-smear grades (2 vs 3, $P < .001$), time to detection of Mtb culture growth (10 [IQR 6–13] versus 6 [IQR 4–9] days, $P < .008$), GeneXpert Ct (24.3 [IQR 19.2–28.3] versus 18.7 [IQR 17.4–22.7], $P = .001$) and grade (3 vs 4, $P = .004$), and lower CRP levels (13.8 [IQR 2.6–33.4] versus 62.5 [IQR 23.1–98.4] mg/dL, < 0.001) (Supplementary Table 3).

When we combined CAC-negative participants from both PCF and ACF cohorts, CAC-positive participants were more likely to report a cough (100% [n = 55] versus 92% [192/208], $P = .03$) and fever (82% [45/55] versus 68% [142/208], $P = .049$) (Table 2). Chest pain was more common among CAC-positive participants (84% [46/55] versus 67% [140/208], $P = .02$) (Table 2). We found that CAC-positive participants were more likely to have more advanced TB based on radiographic features, bacillary burden, and inflammatory markers (Table 2).

Evaluation of the Impact of Differing Eligibility Criteria Between ACF and PCF Cohorts

In sensitivity analyses excluding participants in the ACF cohort with negative or trace Xpert (and culture-confirmed) results, the observed associations remained (Supplementary Tables 4 and 5).

QuantiFERON-Plus Results in HHCs

To investigate differences in TB transmission, we evaluated the HHCs' QFT status by index case-finding and CAC status. The baseline characteristics of HHC did not differ according to the CAC status of the index participant (Supplementary Table 6). After excluding indeterminate (n = 16) and missing results (n = 29), 63% (169/270) of all HHCs were QFT-positive, and this did not differ by index participant case-finding status or other measures of bacillary burden (Table 3). However, HHC QFT status differed by index CAC status: 89% (33/37) of CAC-positive versus 56% (96/172) of CAC-negative ($P < .0001$) (Table 3). Median interferon-γ levels were highest among HHCs of CAC-positive (3.14, IQR 0–5.58) compared to CAC-negative participants (0.085, IQR −0.12 to 2.49) ($P < .001$) (Supplementary Figure, Supplementary table 6). As

Table 2. Baseline Characteristics of Participants Overall and by Cough Aerosol Culture (CAC) Status

	CAC+ Confirmed TB n = 55	CAC− Confirmed TB n = 208	*P* Value[a]	Total n = 263
Baseline characteristics of index participants				
Age, years median [IQR]	29.8 [24.5–37.8]	35.6 [27.5–45.1]	**.006**	33.5 [26.9–43.5]
Women (n, %) (n, %)	10 (18.2%)	59 (28.4%)	.13	69 (26.2%)
Living with HIV	5 (9.1%)	27 (13.0%)	.43	32 (12.2%)
On ART (n, %)	4/5 (80.0%)	12/27 (44.4%)	.14	16/32 (50.0%)
CD4 count, cells/mm^3, median [IQR][b]	204 [150–235] n = 5	129 [57.5–292] n = 24	.75	150 [62–299] n = 29
Previous history of TB (n, %)	9 (16.7%)	39 (18.8%)	.68	48 (18.3%)
Tobacco use (current smoker) (n, %)	10 (18.2%)	39 (18.8%)	.92	49 (18.6%)
Alcohol use (>0 drinks) (n, %)	23 (42.9%)	91/207 (44.0%)	.78	114/262 (43.5%)
Heavy alcohol use (≥5 drinks/day) (n, %)	5/23 (21.7%)	20/91 (22.0%)	.98	25/114 (21.9%)
Symptomatology and healthcare seeking				
Reported cough, any duration (n, %)	55 (100%)	192 (92.3%)	**.03**	247 (93.9%)
Cough ≥ 2 wk (n, %)	52 (94.6%)	188/192 (97.9%)	.18	240/247 (97.2%)
Cough duration, wk, median [IQR][c]	8 [4–12]	8 [4–14]	.91	8 [4–14]
Fever (n, %)	45 (81.8%)	142 (68.3%)	**.049**	187 (71.1%)
Weight loss (n, %)	51 (92.7%)	170/207 (82.1%)	**.05**	221/262 (84.4%)
Night sweats (n, %)	45 (81.8%)	156 (75.0%)	.29	201 (76.4%)
Number of WHO symptoms (n, %)				
0	0 (0%)	6 (2.9%)	**.03**	6 (2.3%)
1	2 (3.6%)	10 (4.8%)		12 (4.6%)
2	6 (10.9%)	32 (15.4%)		38 (14.5%)
3	6 (10.9%)	54 (26.0%)		60 (22.8%)
4	41 (74.6%)	106 (51.0%)		147 (55.9%)
Chest pain (n, %)	46 (83.6%)	140 (67.3%)	**.02**	186 (70.7%)
Previously sought healthcare for symptoms? (n, %)	50 (90.9%)	166 (79.8%)	.06	216 (82.1%)
One visit	30/50 (60.0%)	119/166 (71.7%)	.22	149/216 (69.0%)
Two visits	11/50 (22.0%)	30/166 (18.1%)		41/216 (19.0%)
Three visits	9/50 (18.0%)	17/166 (10.2%)		26/216 (12.0%)
Place healthcare sought? (n, %)				
County hospital	14/50 (28.0%)	49/166 (29.5%)	.84	63/216 (29.2%)
Peripheral health facility	36/50 (72.0%)	121/166 (72.7%)	.90	157/216 (72.7%)
Pharmacy	2/50 (4.0%)	2/166 (1.2%)	.20	4/216 (1.9%)
Traditional healer	0/50 (0%)	0/166 (0%)	-	0/216 (0%)
Private practitioner	6/50 (12.0%)	3/166 (1.8%)	**.002**	9/216 (4.2%)
Other	0/50 (0%)	3/168 (1.8%)	.34	3/216 (1.4%)
Radiographic and laboratory evaluation				
CXR cavitary disease (n, %)	44 (80.0%)	121 (58.2%)	**.003**	165 (62.7%)
CXR quadrants (n, %)				
0	1 (1.8%)	7 (3.4%)	**.008**	8 (3.9%)
1	11 (20.0%)	88 (42.3%)		99 (37.6%)
2	21 (38.2%)	66 (31.7%)		87 (33.1%)
3	17 (30.9%)	29 (13.9%)		46 (17.5%)
AFB-smear positive (n, %)	53 (96.4%)	190 (92.7%)	**.33**	243/260 (93.5%)
AFB-smear grading				
Negative	2 (3.6%)	15/205 (7.3%)	**.04**	17/260 (6.5%)
Positive, Scanty	3 (5.5%)	24/205 (11.7%)		27/260 (10.4%)
Positive, 1+	8 (14.6%)	51/205 (24.9%)		59/260 (22.7%)
Positive, 2+	19 (34.6%)	37/205 (18.1%)		56/260 (21.5%)
Positive, 3+	23 (41.8%)	78/205 (38.1%)		101/260 (38.9%)
Sputum culture (n, %)				
Negative	1 (1.8%)	10/205 (4.9%)	.39	11/260 (4.2%)
Positive—Mtb	54 (98.2%)	188/205 (91.7%)		242/260 (93.1%)

Table 2. Continued

	CAC+ Confirmed TB n = 55	CAC− Confirmed TB n = 208	*P* Value[a]	Total n = 263
MOTT	0 (0%)	2/205 (1.0%)		2/260 (0.8%)
Contaminated	0 (0%)	5/205 (2.4%)		5/260 (1.9%)
Days to Mtb detection in MGIT, median [IQR]	4 [3–5] n = 54	7 [4–10] n = 188	**< .001**	6 [4–9] n = 242
Xpert grade (n, %)				
Negative	0 (0%)	0 (0%)	**.001**	0 (0%)
Trace	0 (0%)	10 (4.8%)		10 (3.8%)
Very Low	1 (1.8%)	16 (7.7%)		17 (6.5%)
Low	3 (5.5%)	46 (22.1%)		49 (18.6%)
Medium	17 (30.9%)	58 (27.9%)		75 (28.5%)
High	34 (61.8%)	78 (37.5%)		112 (42.6%)
Xpert Ct value median [IQR]	17.1 [15.2–18]	19.1 [17.4–23.9]	**< .001**	18.3 [17.1–22.4]
CRP, median [IQR]	88.1 [53.6–119.6]	52.9 [15.9–93.4] n = 206	**< .001**	62.1 [23.8–100.8] n = 261
WBC, median [IQR]	7.7 [6.4–10.1]	7.1 [5.6–9.1] n = 206	**.04**	7.2 [5.8–9.2] n = 261
Hgb, median [IQR]	13 [12.1–14.0]	13.3 [11.8–14.6] n = 206	.33	13.1 [11.9–14.5] n = 261
HbA1c, median [IQR]	5.8 [5.5–6.2]	5.8 [5.4–6.1] n = 205	.75	5.8 [5.5–6.1] n = 260

Abbreviations: AFB, acid-fast bacilli; ART, antiretroviral therapy; CAC−, negative cough aerosol culture; CAC+, positive cough aerosol culture; CRP, C-reactive protein; CXR, chest X-ray; Hgb, hemoglobin; IQR, interquartile range; MOTT, Mycobacterium other than tuberculosis; Mtb, *Mycobacterium tuberculosis*; TB, tuberculosis; WBC, white blood cells; WHO, World Health Organization. The bold values are factors meeting statistical significance at $P < .05$.

[a]*P* values are used to compare the CAC+ and CAC− with confirmed TB from the PCF and ACF cohorts. The Wilcoxon rank-sum test was used to compare medians of continuous variables between the CAC+ and CAC− groups, and chi-squared tests were used to compare proportions.

[b]Limited CD4 counts available, CAC+ n = 5, CAC− n = 22, trace n = 4, total n = 31.

[c]Cough durations only available for some participants: CAC+ n = 55, CAC− n = 192, total n = 247.

QFT-positive results in children are more frequently associated with recent TB exposure, we evaluated QFT status among pediatric HHCs (≤10 years). Similar to all HHCs, QFT-positive status was higher among pediatric HHCs of CAC-positive (88%, 14/16) compared to CAC-negative (45%, 25/56) participants ($P = .01$) (Table 3). We investigated predictors of positive QFT results in HHCs, including index case infectiousness measures (based on CAC results and other measures of bacillary burden). Index CAC-positive status (adjusted odds ratio [aOR] 11.2, 95% CI, 2.2–58.3), index HIV-positive status (aOR 0.1, 95% CI, .0–.6), and HHCs age (aOR 1.04, 95% CI, 1.01–1.08) independently predicted HHCs QFT-positive status (Table 4). The same associations were observed in sensitivity analyses, in which we considered all missing CAC results negative and positive (Supplementary Tables 7 and 8).

DISCUSSION

In adults with PTB identified through different case-finding methods in Nairobi, Kenya, we investigated their clinicodemographic and microbiologic characteristics, CAC status, and the IGRA status of their HHCs. Overall, a higher symptom burden was associated with a higher bacillary burden. Compared to persons identified through PCF, those identified through ACF had fewer TB-related symptoms, lower measures of bacillary burden, and less severe disease; no ACF participants had CAC-positive TB. Interestingly, although traditional clinical markers of infectiousness and CAC status supported greater infectiousness of PCF participants, only CAC status was associated with the IGRA status of HHCs.

Although a substantial proportion of transmission is attributed to persons with subclinical TB [26], evidence is lacking on the infectiousness of community dwellers with undiagnosed TB, many of whom are asymptomatic. A recent meta-analysis determined that 23% of persons with TB who denied cough were AFB smear-positive [7], and a study from Uganda observed that 16% of individuals diagnosed with TB through ACF were AFB smear-positive compared to 53% diagnosed through PCF [12]. The only other study to perform CASS on persons identified with TB through ACF collected sputum from South African adults with at least 1 TB symptom for ≥2 weeks or HIV infection and found that 12 of 51 participants (24%) were CAC-positive [15]. Although this setting had a higher prevalence of TB and HIV than our study setting and the eligibility criteria differed, our results that no ACF participants were CAC-positive is unexpected. In prior studies using CASS-based evaluations in PCF-identified participants, the frequency of CAC-positive persons was 20%–40% [17, 23, 27]. Our findings suggest that persons with CAC-positive TB are uncommon when all people with TB are considered. If true, identifying and treating

Table 3. Baseline QFT Result by Case-finding Status, Index Cough Aerosol Culture, and Other Measures of Bacillary Burden

Characteristics of Index TB Participants	HHC QFT-Plus Results: All HHC (N = 270) Negative QFT (N = 101) (n, %)	HHC QFT-Plus Results: All HHC (N = 270) Positive QFT (N = 169) (n, %)	*P* Value[a]
Index case finding approach (N = 270)			.92
ACF	8/22 (36.4%)	14/22 (63.6%)	
PCF	93/248 (37.5%)	155/248 (62.5%)	
Index CAC (N = 209)			**<.0001**
Positive	4/37 (10.8%)	33/37 (89.2%)	
Negative	76/172 (44.2%)	96/172 (55.8%)	
CAC positivity by CFU (N = 209)			**.001**
High aerosols (≥10 CFU)	4 (14.8%)	23 (85.2%)	
Low aerosols (<10 CFU)	0 (0%)	10 (100%)	
Negative aerosols	76 (44.2%)	96 (55.8%)	
AFB-smear positive	91/243 (37.5%)	152/243 (62.6%)	.92
AFB-smear grading			.16
Negative	10/26 (38.5%)	16/26 (61.5%)	
Positive, scanty	8/23 (34.8%)	15/23 (65.2%)	
Positive, 1+	30/72 (41.7%)	42/72 (58.3%)	
Positive, 2+	25/51 (49.0%)	26/51 (51.0%)	
Positive, 3+	28 (28.9%)	69/97 (71.1%)	
Days to Mtb detection in MGIT, median [IQR]	7 [4–11] n = 98	6 [4–8] n = 162	.06
Xpert grade			.32
Negative	4 (23.5%)	13 (76.5%)	
Trace	8 (36.4%)	14 (63.6%)	
Very low	22 (47.8%)	24 (52.2%)	
Low	40 (39.6%)	61 (60.4%)	
Medium	27 (32.1%)	57 (67.9%)	
Xpert Ct value, median [IQR]	20.1 [17.5–25.7] n = 100	18.2 [16.5–23.9] n = 167	.08
	HHC <10 y (N = 93) Negative QFT (N = 42)	HHC <10 y (N = 93) Positive QFT (N = 51)	
Index case finding approach			.22
ACF	3/4 (75.0%)	1/4 (25.0%)	
PCF	39/89 (43.8%)	50/89 (56.2%)	
Index CAC (N = 72)			**.01**
Positive	2/16 (12.5%)	14/16 (87.5%)	
Negative	31/56 (55.4%)	25/56 (44.6%)	

Abbreviations: ACF, active case-finding; AFB, acid-fast bacilli; CAC, cough aerosol culture; CFU, colony-forming units; Mtb, *Mycobacterium tuberculosis*; PCF, passive case-finding; QFT, QuantiFERON-Plus; TB, tuberculosis. The bold values are factors meeting statistical significance at $P < .05$.

[a]Chi-squared tests to compare proportions.

community-dwellers with TB likely to progress to CAC-positive TB would be an important intervention for ending TB.

It is estimated that up to 80% of transmission events in TB-endemic settings occur outside of the household [28, 29]. We found that CAC status, but not the case-finding method, was associated with HHC IGRA status. We are unable to assess whether the frequency of IGRA-positive results among CAC-negative households is higher than our estimates for Nairobi adults without known TB exposure (~50%, based on evaluations of lower risk [ie, salaried government employees] and higher risk groups [ie, HIV clinic attendees]) [17]. While TB transmission modeling studies suggest that highly infectious persons (ie, CAC-positive) may individually transmit more TB but that the high burden of subclinical TB leads to asymptomatic persons as significant drivers of population-level transmission events, direct evidence is lacking [26]. Household TB transmission may differ from transmission through casual contact outside the household. It is possible that CAC-positive TB may be more likely to drive TB transmission in the community due to greater aerosolization of infectious particles that may be less dependent on proximity and duration of contact; studies are needed to address this among the many knowledge gaps related to TB transmission.

Table 4. Mixed-effects Regression Analyses of Index and Household Contact Characteristics Associated With QFT Results in Household Contacts (Excluding Indeterminate Results)

Predictors of QFT Positivity[b]	OR	95% CI	*P* Value	aOR[b]	95% CI	*P* Value
Characteristics of household contacts (N = 209)						
Age, y	1.04	1.01–1.08	**.004**	1.04	1.01–1.08	**.004**
Women	1.10	.52–2.30	.81	-	-	-
BMI, kg/m^2 (N = 207)	1.11	1.02–1.20	**.02**	-	-	-
MUAC, cm (N = 207)	1.11	1.03–1.20	**.01**	-	-	-
Living with HIV (N = 128)	1.59	.25–10.06	.63	…	…	…
Characteristics of index TB participants with whom household contacts resided (N = 209)						
CAC+	12.58	2.11–39.36	**.003**	11.42	2.05–63.76	**.006**
Case finding status	…	…		-	-	-
PCF	Ref	…				
ACF	1.10	.24–4.77	.90			
Age, y	1.01	.98–1.05	.58	-	-	-
Women	0.97	.36–2.59	.95	-	-	-
Living with HIV	0.16	.04–.65	**.01**	0.17	.04–.83	**.028**
Xpert Ct	1.00	.92–1.07	.91	-	-	-
Xpert grade[a]	1.06	.71–1.59	.77	-	-	-
Smear grade[††] (N = 208)	1.10	.76–1.58	.62	-	-	-
Sputum culture (N = 208)	…	…		-	-	-
Positive—Mtb	0.86	.10–7.68	.89			
TTD (d) (N = 199)	0.89	.79–.99	**.04**	-	-	-
Cavitary CXR	1.63	.63–4.20	.31	-	-	-
CXR quadrants	1.70	.98–2.95	.06	-	-	-
CRP (N = 205)	1.01	.99–1.02	.27	-	-	-
HHC for each index (N = 181)	1.22	.93–1.62	.15	-	-	-

Abbreviations: aOR, adjusted odds ratio; CAC–, negative cough aerosol culture; CAC+, positive cough aerosol culture; CI, confidence interval; CRP, C-reactive protein; CXR, chest X-ray; PCF, passive case finding; QFT, QuantiFERON Result; TB, tuberculosis; TTD, time to detection of Mtb growth in liquid media. The bold values are factors meeting statistical significance at $P < .05$.

[a]Semiquantitative Xpert grade from 0 (neg) to 5 (high).

[b]Mixed effects analysis, multivariate analysis using forward selection stepwise regression method included factors with $P < .05$ excluding HHC MUAC due to evidence of collinearity with age and BMI. We retained covariates that significantly improved model fit based on likelihood-ratio tests, reported in the last column.

[††]Semiquantitative smear grade from 0 (neg) to 4 (positive, 3+).

Symptom-based screening tools are currently the foundation of TB case-finding, and simple, cost-effective screening tools are needed [30]. Consistent with subclinical TB definitions [7], 27% of the ACF cohort denied all WHO screening symptoms. Our findings of an association between symptom and bacillary burden among all participants with confirmed TB suggest opportunities to enhance symptom screen sensitivity. Symptom screens that focus on persons with TB most likely to progress to highly infectious states may support cost-effective interventions to decrease TB transmission.

We found that delays in diagnosis occurred despite participants' seeking healthcare, in keeping with previous findings from other regions [31] and Kenya [18, 32]. In the 2015–16 Kenya National TB Prevalence Survey, 21% of the survey participants with TB had previously sought healthcare, mostly in private facilities [18]. In contrast, most prior healthcare visits in our study occurred at higher tiers of the public healthcare system where provider education, diagnostics, and algorithms could be enhanced to improve TB diagnosis. Variation in the capacity for TB diagnosis across counties and facility levels in Kenya has been reported previously [33]. These findings suggest that improving the care cascade for symptomatic persons is still an important research area.

Our study has limitations, including differences in eligibility, which may have introduced bias in comparing 2 groups (ACF and PCF) with different eligibility criteria (ACF could have a positive culture or Ultra test, whereas PCF first needed a positive Ultra test). However, because our goal is to investigate the infectiousness of community dwellers with undiagnosed TB to persons who present for healthcare, this is less of a limitation. In addition, the observed associations remained in sensitivity analyses, where we excluded ACF participants with Xpert Ultra negative sputum results. Fewer index cases and HHCs were enrolled through ACF, and not all the participants underwent the CASS procedures, reducing the likelihood of detecting differences. In addition, although we found a greater frequency of women diagnosed with TB through ACF, our community-based prevalence survey disproportionately enrolled women, and we were not able to determine differences by case-finding method. IGRAs to test for Mtb may not identify recent versus remote infection. Our study has several strengths, including using CASS to measure infectiousness and IGRA results to measure HHC Mtb infection as a transmission marker in HHCs, including pediatric HHCs.

In conclusion, our findings suggest that highly infectious persons (CAC-positive) with TB are uncommon among prevalent cases of TB in the community.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Availability of data and material. The data underlying this article will be shared on reasonable request to the corresponding author.

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References

1. World Health Organization. Global tuberculosis report 2023. Geneva: World Health Organization, **2023**. Licence: CC BY-NC-SA 3.0 IGO.
2. Coussens AK, Zaidi SMA, Allwood BW, et al. Classification of early tuberculosis states to guide research for improved care and prevention: an international Delphi consensus exercise. Lancet Respir Med **2024**; 12:484–98.
3. Ayles H, Muyoyeta M, Du Toit E, et al. Effect of household and community interventions on the burden of tuberculosis in Southern Africa: the ZAMSTAR community-randomised trial. Lancet **2013**; 382:1183–94.
4. Klinkenberg E, Floyd S, Shanaube K, et al. Tuberculosis prevalence after 4 years of population-wide systematic TB symptom screening and universal testing and treatment for HIV in the HPTN 071 (PopART) community-randomised trial in Zambia and South Africa: a cross-sectional survey (TREATS). PLoS Med **2023**; 20:e1004278.
5. Marks GB, Nguyen NV, Nguyen PTB, et al. Community-wide screening for tuberculosis in a high-prevalence setting. N Engl J Med **2019**; 381:1347–57.
6. Drain PK, Bajema KL, Dowdy D, et al. Incipient and subclinical tuberculosis: a clinical review of early stages and progression of infection. Clin Microbiol Rev **2018**; 31:e00021-18.
7. Stuck L, Klinkenberg E, Abdelgadir Ali N, et al. Prevalence of subclinical pulmonary tuberculosis in adults in community settings: an individual participant data meta-analysis. Lancet Infect Dis **2024**; 24:726–36.
8. Frascella B, Richards AS, Sossen B, et al. Subclinical tuberculosis disease-a review and analysis of prevalence surveys to inform definitions, burden, associations, and screening methodology. Clin Infect Dis **2021**; 73:e830–41.
9. Asadi L, Croxen M, Heffernan C, et al. How much do smear-negative patients really contribute to tuberculosis transmissions? Re-examining an old question with new tools. EClinicalMedicine **2022**; 43:101250.
10. Jones-Lopez EC, Namugga O, Mumbowa F, et al. Cough aerosols of Mycobacterium tuberculosis predict new infection: a household contact study. Am J Respir Crit Care Med **2013**; 187:1007–15.
11. Sultan L, Nyka W, Mills C, O'Grady F, Wells W, Riley RL. Tuberculosis disseminators. A study of the variability of aerial infectivity of tuberculous patients. Am Rev Respir Dis **1960**; 82:358–69.
12. Kendall EA, Kitonsa PJ, Nalutaaya A, et al. The spectrum of tuberculosis disease in an urban Ugandan community and its health facilities. Clin Infect Dis **2021**; 72: e1035–43.
13. Martinez L, Woldu H, Chen C, et al. Transmission dynamics in tuberculosis patients with human immunodeficiency virus: a systematic review and meta-analysis of 32 observational studies. Clin Infect Dis **2021**; 73:e3446–55.
14. Nguyen HV, Tiemersma E, Nguyen NV, Nguyen HB, Cobelens F. Disease transmission by patients with subclinical tuberculosis. Clin Infect Dis **2023**; 76:2000–6.
15. Esmail A, Randall P, Oelofse S, et al. Comparison of two diagnostic intervention packages for community-based active case finding for tuberculosis: an open-label randomized controlled trial. Nat Med **2023**; 29:1009–16.
16. Van't Hoog AH, Marston BJ, Ayisi JG, et al. Risk factors for inadequate TB case finding in rural Western Kenya: a comparison of actively and passively identified TB patients. PLoS One **2013**; 8:e61162.
17. Nduba V, Njagi LN, Murithi W, et al. Mycobacterium tuberculosis cough aerosol culture status associates with host characteristics and inflammatory profiles. Nat Commun **2024**; 15:7604.
18. Enos M, Sitienei J, Ong'ang'o J, et al. Kenya tuberculosis prevalence survey 2016: challenges and opportunities of ending TB in Kenya. PLoS One **2018**; 13: e0209098.
19. WHO consolidated guidelines on tuberculosis. Module 3: diagnosis—rapid diagnostics for tuberculosis detection. 3rd ed. Geneva: World Health Organization, **2024**. Licence: CC BY-NC-SA 3.0 IGO. Available at: https://www.who.int/publications/i/item/9789240089501.
20. Chakravorty S, Simmons AM, Rowneki M, et al. The new Xpert MTB/RIF ultra: improving detection of mycobacterium tuberculosis and resistance to rifampin in an assay suitable for point-of-care testing. mBio **2017**; 8:29.
21. Fennelly KP, Jones-López EC, Ayakaka I, et al. Variability of infectious aerosols produced during coughing by patients with pulmonary tuberculosis. Am J Respir Crit Care Med **2012**; 186:450–7.
22. Fennelly KP, Martyny JW, Fulton KE, Orme IM, Cave DM, Heifets LB. Cough-generated aerosols of Mycobacterium tuberculosis: a new method to study infectiousness. Am J Respir Crit Care Med **2004**; 169:604–9.
23. Theron G, Limberis J, Venter R, et al. Bacterial and host determinants of cough aerosol culture positivity in patients with drug-resistant versus drug-susceptible tuberculosis. Nat Med **2020**; 26:1435–43.
24. QuantiFERON-TB Gold Plus (QFT-Plus). ELISA package insert 02/2016. n.d. Available at: http://www.quantiferon.com/wp-content/uploads/2017/04/English_QFTPlus_ELISA_R04_022016.pdf (Accessed 15 April 2021).
25. WHO Consolidated guidelines on tuberculosis: module 5: management of tuberculosis in children and adolescents [internet]. Geneva: World Health Organization, **2022**. Table 3, WHO recommendations on TB screening and contact investigation relevant to children and adolescents. Available at: https://www.ncbi.nlm.nih.gov/books/NBK579379/table/ch2.tab1/.
26. Emery JC, Dodd PJ, Banu S, et al. Estimating the contribution of subclinical tuberculosis disease to transmission: an individual patient data analysis from prevalence surveys. Elife **2023**; 12:e82469.
27. Acuña-Villaorduña C, Ayakaka I, Schmidt-Castellani LG, et al. Host determinants of infectiousness in smear-positive patients with pulmonary tuberculosis. Open Forum Infect Dis **2019**; 6:ofz184.
28. Verver S, Warren RM, Munch Z, et al. Proportion of tuberculosis transmission that takes place in households in a high-incidence area. Lancet **2004**; 363:212–4.
29. Coleman M, Martinez L, Theron G, Wood R, Marais B. Mycobacterium tuberculosis transmission in high-incidence settings-new paradigms and insights. Pathogens **2022**; 11:1228.
30. World Health Organization. WHO operational handbook on tuberculosis module 2: screening—systematic screening for tuberculosis disease [Handbook]. 2020 [updated 22 March 2021]. Available at: https://www.who.int/publications/i/item/9789240022614 (Accessed 20 April 2024).
31. Shah HD, Nazli Khatib M, Syed ZQ, et al. Gaps and interventions across the diagnostic care cascade of TB patients at the level of patient, community and health system: a qualitative review of the literature. Trop Med Infect Dis **2022**; 7:136.
32. Tollefson D, Ngari F, Mwakala M, et al. Under-reporting of sputum smear-positive tuberculosis cases in Kenya. Int J Tuberc Lung Dis **2016**; 20:1334–41.
33. Masini E, Hanson C, Ogoro J, et al. Using patient-pathway analysis to inform a differentiated program response to tuberculosis: the case of Kenya. J Infect Dis **2017**; 216:S714–s23.