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In-home TB Testing Using GeneXpert Edge is Acceptable, Feasible, and Improves the Proportion of Symptomatic Household Contacts Tested for TB: A Proof-of-Concept Study

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Background. Household contact investigations are effective for finding tuberculosis (TB) cases but are hindered by low referral uptake for clinic-based evaluation and testing. We assessed the acceptability and feasibility of in-home testing of household contacts (HHC) using the GeneXpert Edge platform.

Methods. We conducted a 2-arm, randomized study in Eastern Cape, South Africa. HHCs were verbally assessed using the World Health Organization-recommended 4-symptom screen. Households with ≥1 eligible symptomatic contact were randomized. Intervention households received in-home GeneXpert MTB/RIF molecular testing. GeneXpert-positive HHCs were referred for clinic-based treatment. Standard-of-care households were referred for clinic-based sputum collection and testing. We defined acceptability as agreeing to in-home testing and feasibility as generation of valid Xpert MTB/RIF results. The proportion and timeliness of test results received was compared between groups.

Results. Eighty-four households were randomized (n = 42 per arm). Of 100 eligible HHCs identified, 98/100 (98%) provided consent. Of 51 HHCs allocated to the intervention arm, all accepted in-home testing; of those, 24/51 (47%) were sputum productive and 23/24 (96%) received their test results. Of 47 HCCs allocated to standard-of-care, 7 (15%) presented for clinic-based TB evaluation, 6/47 (13%) were tested, and 4/6 (67%) returned for their results. The median (interquartile range) number of days from screening to receiving test results was 0 (0) and 16.5 (11-15) in the intervention and standard-of-care arms, respectively.

Conclusions. In-home testing for TB was acceptable, feasible, and increased HHCs with a molecular test result. In-home testing mitigates a major limitation of household contact investigations (dependency on clinic-based referral), revealing new strategies for enhancing early case detection.

Keywords. active case finding; geneXpert; point-of-care testing; South Africa; tuberculosis.

Tuberculosis (TB) continues to be 1 of the leading infectious global cause of death, with recent increases in both incidence and mortality [1]. The TB cascade helps to quantify gaps in care delivery, providing a context-specific overview of time points vulnerable to disengagement in care. Diagnosis is the weakest link in the cascade of TB care [2]. Molecular testing has improved case detection [3] but structural barriers (eg, access) [4], health care-seeking behaviors [5], and health system weaknesses (eg, failure to identify and/or test symptomatic individuals) [6] continue to undermine the impact of new technologies.

On a fundamental level, a major limitation to current diagnostic approaches is their centralized and passive nature (ie, people need to go to health facilities to access testing) [7–10]. Active case finding (ACF) has been increasingly recognized as an important and complementary strategy to passive case finding in high-prevalence settings to overcome the gaps in TB detection and treatment [11–13]. ACF is a proactive strategy that identifies people with TB who may not be detected by the health system or do not self-report to a health care

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facility [14]. The lack of mobile, point-of-care tests for TB has limited ACF approaches by necessitating centralized diagnostic testing. Two recent studies have explored the feasibility and effectiveness of integrating TB molecular diagnostic platforms into mobile vans and river boats to intensify case finding and testing among poorly served populations [3, 15]. Unfortunately, both studies continued to rely on passive presentation to these community-based testing sites. To improve case detection, targeted ACF and decentralized molecular testing must be implemented and scaled up [16, 17].

Household contacts (HHCs) of TB index patients are at high risk of TB and are a key population in need of expanded ACF strategies [18]. Household contact investigation (HCI) is an effective intervention to improve early case detection [11] but is often undermined by low uptake of community-to-clinic referrals for further clinical evaluation, including diagnostic testing [19–21]. By bringing diagnostic services into households (ie, true decentralization), barriers associated with low referral uptake could be overcome.

Our qualitative work showed in-home testing of HHCs using GeneXpert Edge was highly acceptable, mitigated apathy and negative perceptions of clinic-based testing, and was perceived to improve household and community-level health insecurities [22]. Here, we present quantitative findings from a pilot randomized study investigating the acceptability and feasibility of in-home TB testing in the Eastern Cape Province, South Africa.

METHODS

Study Design and Setting

A 2-arm randomized study was conducted from 23 July 2018 to 18 May 2019 in Duncan Village, Buffalo City Metro Health District, Eastern Cape Province, South Africa. In 2019, Buffalo City Metro had an estimated TB incidence of 876 cases per 100 000 population [23].

Index Case Recruitment

People diagnosed with pulmonary TB were recruited from within 6 government health clinics [22] using the following eligibility criteria: (1) age ≥ 18 years; (2) reside in Duncan Village; (3) share a living space with other people; (4) did not already have HCI conducted; and (5) willingness to provide informed consent. Research staff administered a questionnaire using Research Electronic Data Capture [24, 25]. Index cases were asked to provide a list of household members with member names and their contact information and to notify household members of the pending HCI. HCIs were scheduled for 3 to 4 days later. A household was defined as a group of people that reside on the same plot of land and share the same address [26] and a HHC was defined per the World Health Organization [27].

Household Contact Recruitment

HCI methods have been previously described [22]. Briefly, HHCs verbally consented to be screened using the World Health Organization-recommended, 4-symptom screen for TB in accordance with South African national guidelines [28]. Households with at least 1 symptomatic individual were then invited to participate with the following inclusion criteria for individual members: (1) symptomatic per South African national guidelines; (2) age ≥ 18 years; (3) not on TB treatment; and (4) willing to provide written informed consent. Ineligible or nonconsenting symptomatic individuals were referred to a local clinic for further clinical evaluation. Consenting household members were administered a study questionnaire. Households were not financially compensated for their time but were provided a small snack and drink box (<$1 USD) while completing study activities (snacks provided after sputum collection in the intervention).

Household Randomization

Using the built-in randomization module in Research Electronic Data Capture from a computer pregenerated list of permuted blocks of 16, households with at least 1 eligible HHC were randomized 1:1 to: (1) in-home testing with treatment referral (intervention) or (2) in-home screening with testing referral (standard-of-care [SoC]).

In-home TB Testing (Intervention Arm)

Participants were instructed on how to provide high-quality sputum per South African national guidelines [28]. Individuals unable to produce sputum were referred to the clinic for further clinical evaluation. Sputum collection was performed in a safe, private, and well-ventilated area (typically outdoors). Sputum was immediately processed in homes and tested using Xpert MTB/RIF (Xpert) on GeneXpert Edge (Cepheid, Sunnyvale, CA) per manufacturer's recommendations [29].

Referrals for Clinic-based TB Services

Contacts with an Xpert-positive test result were immediately referred to their preferred local clinic. Xpert-negative symptomatic contacts were referred for further clinical evaluation and testing per South African guidelines [28]. Regardless of study arm, participants were neither escorted nor provided transport/travel support to the clinic. Referral letters were printed on Department of Health letterhead. Referrals did not engender special treatment at the clinic.

Follow-up of Clinic-based Referrals

Study staff at the 6 clinics recorded all people presenting for TB screening, testing, and treatment, and cross-referenced study participants' identifiable information collected from households with clinic registration and TB logs. Regardless of arm, all individuals provided a referral for clinic-based services who had not been identified via cross-referencing within

30 days of referral were contacted via phone or follow-up home visit and asked if they had presented to a clinic. Participants unable to be tracked after 30 days or whose self-reported presentation could not be verified were classified as lost to follow-up or did not seek care, respectively.

Data Management

Data were captured using password-protected electronic tablets and stored on a secure server. Hard copy documents were deidentified with a participant identification number and stored in lockable cabinets in a secure office.

Analysis

Basic descriptive statistics were analyzed using a 2-sample *t*-test, chi-squared test, or analysis of variance. Analyses were significant if alpha was less than .05. Acceptability was a priori defined as ≥80% of symptomatic contacts accepting in-home testing. Feasibility was a priori defined as (1) ≥ 80% of households visited having a suitable space for sputum production and (2) ≥ 95% actionable (positive or negative) Xpert results. Time from screening to receiving of test results was compared across study arms. All analyses were performed with STATA 13.1 (StataCorp, College Station, TX, USA).

Patient Consent Information

Written informed consent was obtained from all study participants. Human research ethics approval was provided by The University of Pretoria Research Ethics Committee (#016/2016), South Africa, and the Eastern Cape Department of Health Provincial Research Committee (EC_2016RP4_118).

RESULTS

Enrollment and Randomization

Index cases: Of 486 index cases screened, 295 (61%) were eligible and 282/295 (96%) provided informed consent (Figure 1). The most common reason for ineligibility was living alone (86/191; 45%). Of those who enrolled, 162/282 (57%) were initiated on TB treatment on the same day of study recruitment, and 120/282 (43%) had initiated treatment before recruitment.

Households and household contacts: From the 282 index cases, 1070 household contacts were listed, of which 906/1070 (85%) were screened. Of those screened, 173/906 (19%) adults and children screened positive for at least 1 TB symptom (data not shown). Of those symptomatic contacts, 100 (58%) were eligible for randomization, and 98/100 (98%) provided informed consent for testing. Those 98 contacts represent 84 households —42 allocated to each arm, yielding 51 and 47 contacts in intervention and SoC, respectively.

Contacts' Characteristics

The median age of HHCs was 40 years (interquartile range [IQR]: 28-52.75), 58/98 (60%) were female, 71/98 (73%) had not completed high school, and 76/98 (78%) reported a monthly income of < ZAR5000 (~$350 USD) (Table 1). Clinically, 27/98 (28%) contacts reported ≥3 symptoms, 31/98 (32%) had previously sought care for their symptoms, and 78/98 (80%) reported having at least 1 symptom for more than 2 weeks. Moreover, 20/98 (20%) self-reported living with HIV and 24/98 (25%) reported prior TB. No significant differences in participant characteristics occurred between arms.

Acceptability and Feasibility of In-home TB Testing

All HHCs randomized to the intervention arm agreed to in-home testing and attempted sputum production, of which 24/51 (47%) successfully produced sputum (Table 2). Of the 24 in-home tests performed, 23 (95.8%) produced actionable results. The median time study staff spent in a home conducting in-home testing was 119 minutes (IQR: 109-210) compared to 33 minutes (IQR: 18-45) among SoC households. A total of 66.7% of households had contacts tested in a single visit with a maximum of up to 3 visits made to each household.

TB Testing Cascade and Referral Uptake

Of the 47 HHC randomized to SoC, 7 (15%) accessed clinic-based TB testing compared to 51/51 (100%) intervention arm participants offered testing in their homes ($P < .0001$) (Figure 2). Of those, 6/47 (13%) SoC participants and 24/51 (47%) intervention arm participants were tested ($P < .0001$); untested intervention arm participants were unable to produce sputum specimens. Among those tested, 4/6 (67%) SoC participants returned to the clinic to receive their test results, compared to 23/24 (96%) intervention arm participants ($P = .0001$) who received same-day test results as part of the HCI; 1 in-home test run produced an invalid test result. The median (IQR) days from screening to receiving test results was 16.5 days (11-25) in SoC, and 0 days in the intervention arm ($P = .0004$). Three individuals in each arm tested positive for TB. Of those who received a positive result, 2/3 (67%) in SoC and 2/3 (67%) in the intervention arm initiated treatment. Of the 2 participants in the SoC arm, treatment was initiated 14 and 39 days after screening, whereas both intervention arm participants with a positive TB test result initiated treatment within 1 day of screening.

DISCUSSION

To our knowledge, this is the first study to implement in-home molecular testing for TB as part of household contact investigations. Our previous qualitative investigations reported that in-home testing was acceptable and feasible [22]. Here, we quantitatively report high acceptability and feasibility using GeneXpert Edge. Our TB testing cascade analysis reveals in-home testing engaged a higher proportion of individuals at every step compared to those referred for clinic-based testing (SoC), overcoming a major limitation associated with ACF.

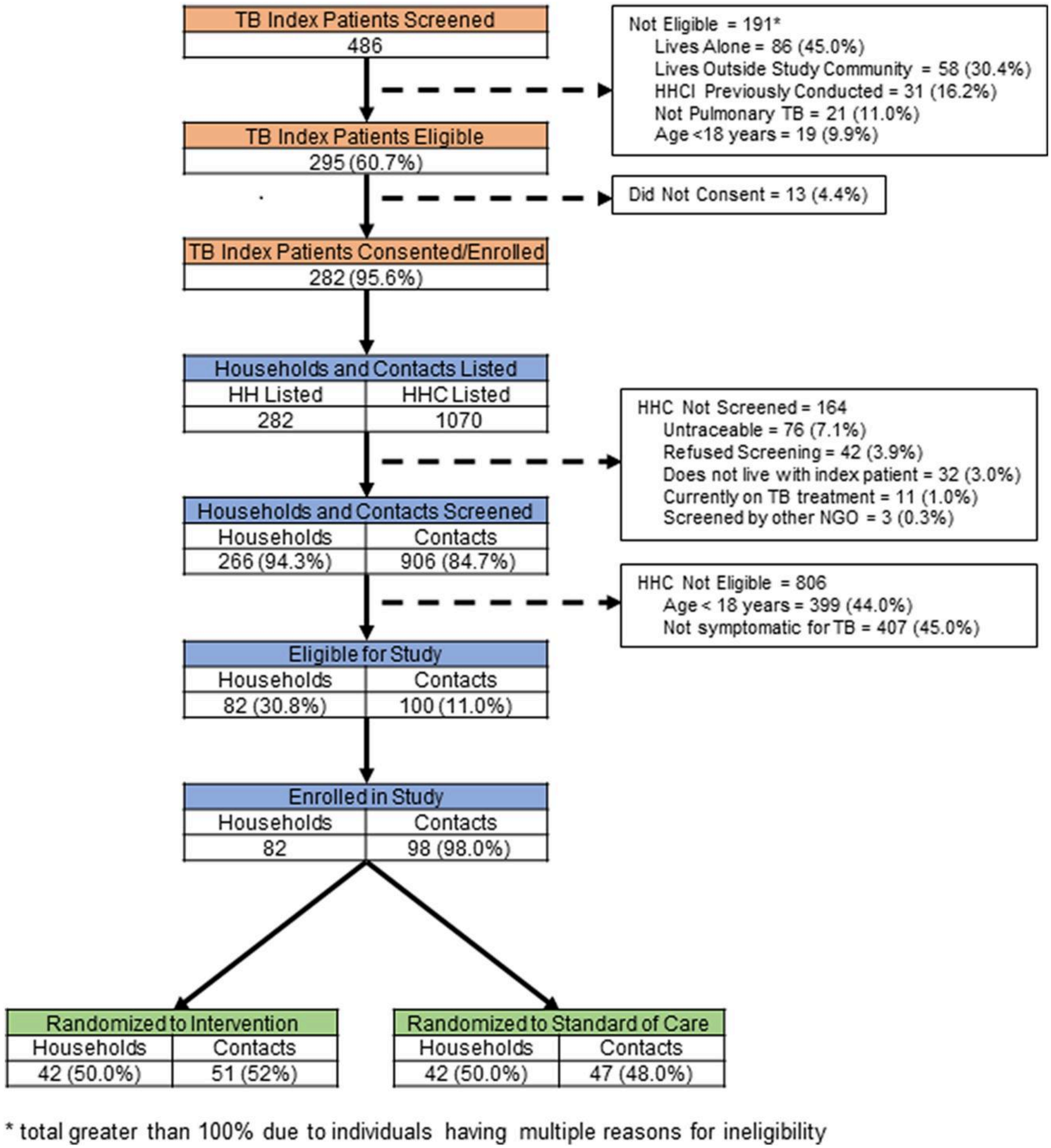

Figure 1. Flow diagram of tuberculosis index patient and household contact enrollment.

Although the number of participants that had a positive result was small, time from screening to receiving test results was shorter for intervention participants compared to those who received SoC, and a negative test result itself carries significant value.

In-home testing for TB may significantly impact the number of people needing testing who actually get tested. Increasing the overall reach of TB testing by removing barriers to accessible testing may facilitate TB control by increasing early TB detection and decreasing time to initiation of treatment. However, applying this model to TB has been—until recently—impossible, as there has not been an effective, mobile molecular technology for rapid diagnosis enabling a result in-home, which itself appears critical for encouraging people who test

Table 1. Characteristics of Randomized Symptomatic Household Contacts

Characteristic		Total n = 98[a] (%)[b]	Randomization Arms[c] Intervention n = 51 (52.6%)	Standard of Care n = 47 (48.5%)	*P* Value
Sociodemographic Data					
Age (IQR)		40 (28-53)	38 (26-49)	41 (30-53)	.28
Sex	Male	39 (40.2%)	20 (51.3%)	19 (48.7%)	.97
	Female	58 (59.8%)	30 (51.7%)	28 (48.3%)	
Population group	Black	85 (87.6%)	45 (52.9%)	40 (47.1%)	.48
	White	1 (1.0%)	0 (0.0%)	1 (100.0%)	
	Missing	11 (12.6%)	5 (45.5%)	6 (54.5%)	
Relationship	Nonunion	57 (58.8%)	30 (52.6%)	27 (47.4%)	.71
	Union	37 (38.1%)	18 (48.7%)	19 (51.4%)	
	Missing	3 (3.1%)	2 (33.3%)	1 (66.7%)	
Education	<grade 12	71 (73.2%)	36 (50.7%)	35 (49.3%)	.86
	High school diploma (grade 12)	23 (23.7%)	12 (52.2%)	11 (47.8%)	
	Tertiary	3 (3.1%)	2 (66.7%)	1 (33.3%)	
Employment	Employed	35 (36.1%)	18 (51.4%)	17 (48.8%)	.96
	Unemployed	62 (63.9%)	32 (51.6%)	30 (48.4%)	
Monthly income	<R5 000	76 (78.4%)	40 (52.6%)	36 (47.4%)	.88
	>R5 000	10 (10.3%)	5 (50.0%)	5 (50.0%)	
	Missing	11 (11.3%)	5 (45.5%)	6 (54.5%)	
Health Characteristics					
TB Symptoms					
Cough	Yes	69 (71.1%)	39 (56.5%)	30 (43.5%)	.12
	No	28 (28.9%)	11 (39.3%)	17 (60.7%)	
Duration of cough	<2 wk	16 (23.2%)	11 (68.8%)	5 (31.3%)	.40
	2 wk—2 mo	48 (69.6%)	26 (54.2%)	22 (45.8%)	
	>2 mo	5 (7.2%)	2 (40.0%)	3 (60.0%)	
Fever	Yes	54 (55.7%)	27 (50.0%)	27 (50.0%)	.73
	No	43 (44.3%)	23 (53.5%)	20 (46.5%)	
Duration of fever	<2 wk	15 (27.8%)	9 (60.0%)	6 (40.0%)	.65
	2 wk—2 mo	36 (66.7%)	17 (47.2%)	19 (52.8%)	
	>2 mo	3 (5.6%)	1 (33.3%)	2 (66.7%)	
Night sweats	Yes	43 (44.3%)	24 (55.8%)	19 (44.2%)	.45
	No	54 (55.6%)	26 (48.2%)	28 (51.9%)	
Duration of night sweats	<2 wk	8 (18.6%)	4 (50.0%)	4 (50.0%)	.91
	2 wk—2 mo	29 (67.4%)	17 (58.6%)	12 (41.4%)	
	>2 mo	6 (14.0%)	3 (50.0%)	3 (50.0%)	
Weight loss	Yes	44 (45.4%)	26 (59.1%)	18 (40.9%)	.18
	No	53 (54.6%)	24 (45.3%)	29 (54.7%)	
Duration of weight loss	<2 wk	5 (11.4%)	3 (60.0%)	2 (40.0%)	1.0
	2 wk—2 mo	29 (65.9%)	17 (58.6%)	12 (41.4%)	
	>2 mo	10 (22.7%)	6 (60.0%)	4 (40.0%)	
# of TB symptoms	1	27 (27.8%)	10 (37.0%)	17 (63.0%)	.38
	2	33 (34.0%)	19 (57.6%)	14 (42.4%)	
	3	19 (19.6%)	12 (63.1%)	7 (36.8%)	
	4	15 (15.5%)	8 (53.3%)	7 (46.7%)	
	Missing data	3 (3.1%)	1 (33.3%)	2 (66.7%)	
Sought care for symptoms	Yes	31 (31.6%)	13 (41.9%)	18 (58.1%)	.17
	No	67 (68.4%)	38 (56.7%)	29 (43.3%)	
Previous history of TB	Never	72 (74.2%)	34 (47.2%)	38 (52.8%)	.18
	Yes, <2 y ago	9 (9.3%)	4 (44.4%)	5 (55.6%)	
	Yes, >2 y ago	15 (15.5%)	11 (73.3%)	4 (26.7%)	
	Missing	1 (1.0%)	1 (100.0%)	0 (.0%)	
HIV	Positive	20 (20.4%)	13 (65.0%)	7 (35.0%)	.45
	Negative	42 (42.9%)	23 (54.8%)	19 (45.2%)	
	Declined to report	36 (36.7%)	14 (38.9%)	22 (61.1%)	

Table 1. Continued

Characteristic	Total n = 98[a] (%)[b]	Randomization Arms[c] Intervention n = 51 (52.6%)	Standard of Care n = 47 (48.5%)	P Value
TB Knowledge				
TB knowledge (scale range: 0-5; IQR)	3 (2)	2 (2)	3 (2)	.25

Abbreviations: IQR, interquartile range; TB, tuberculosis.

[a]Of the 98 household contacts, 1 did not complete a study questionnaire.

[b]Column percentages.

[c]Row percentages.

Table 2. Measurable Characteristics of Acceptability and Feasibility of Intervention Arm In-home Testing

Characteristics		Total
Eligible symptomatic household contacts	…	100
Symptomatic contacts providing consent	…	98 (98%)
Randomized to intervention arm	…	51 (52%)
Sputum Collection (intervention arm only)	Individuals attempting sputum production	51 (100%)
	Total specimens collected	24 (47.1%)
	Spontaneous sputum production	20 (83.3%)
	Induced sputum production	4 (16.7%)
	Sputum not collected	27 (52.9%)
	Couldn't produce	22 (81.5%)
	Didn't have time	1 (3.7%)
	No safe or private space	0 (0%)
	Other	4 (14.8%)
# of household visits needed to collect sputum	1 visit	16 (66.7%)
	2 visits	4 (16.7%)
	3 visits	4 (16.7%)
TB test results	Valid result	23 (95.8%)
	Invalid results/error	1 (4.2%)
Median time spent screening and/or testing in households, min (IQR)[a]	Standard-of-Care	33 (18–45)
	Intervention	119 (109–210)

Abbreviations: IQR, interquartile range; TB, tuberculosis.

[a]Does not include administration of study questionnaire.

positive to start treatment at clinics [22, 30]. Other infectious diseases have shown the effectiveness of in-home testing. For example, in-home HIV testing is an acceptable and effective intervention for learning one's HIV status and providing linking to care [31–33]. Furthermore, in-home testing is increasingly recognized as effective for poorly served populations [34] and for identifying HIV-infected individuals at an earlier stage of disease [35, 36]. Recent developments in TB diagnostics and implementation have seen molecular diagnostic testing move out of the clinic and into community settings, including placing GeneXpert platforms on mobile vans and river boats. [3, 15] Despite these innovative implementation approaches, the present study marks a significant departure as the first to use in-home point-of-care testing for TB. This is particularly noteworthy considering that in-home testing for other infectious diseases has demonstrated higher uptake among individuals who have never been tested before and better linkage to care when compared to mobile testing [37].

As a measure of acceptability, we reported on the number of household contacts that agreed to in-home testing and attempted to produce sputum. We found in-home testing to be highly acceptable. This result aligns with other point-of-care diagnostic studies reporting acceptability rates between 98% and 100% [3, 15]. In terms of feasibility, we reported that >95% of tests run produced a valid test result; our only invalid test result was generated while conducting our first ever in-home test. Though a larger sample size is needed to fully assess how well the Edge platform will perform over time when transported frequently in backpacks and set up in homes with varying environments (ie, dirt floors, temperature, humidity, uneven surfaces), our work further expands the application of molecular diagnostics for ACF approaches, specifically in the context of household contact investigations. It is also notable that a major dropoff in

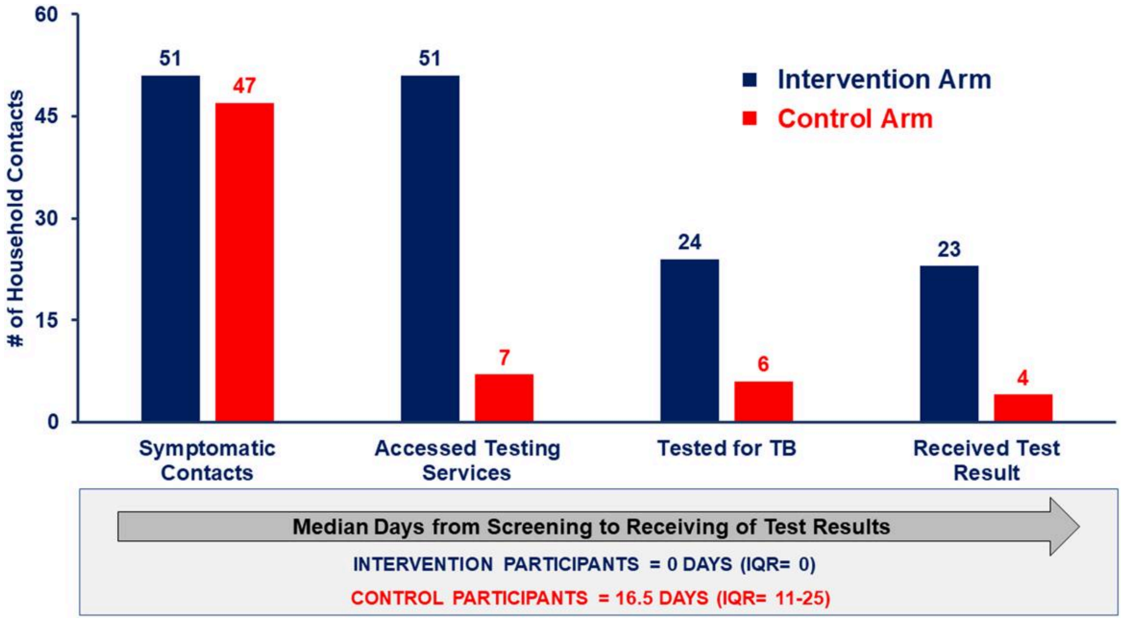

Figure 2. Tuberculosis testing cascade.

testing of intervention arm participants was due to their inability to produce sputum. Quality sputum production remains an inherent limitation of all sputum-based TB diagnostics.

A critical barrier addressed by our study is the challenge of motivating symptomatic household contacts to present to a health facility for evaluation and TB testing, a significant bottleneck of traditional contact investigations that conduct in-home symptom screening and referral for clinic-based TB services [19–21, 38]. Previous household contact investigations have reported successful referral rates between 12% and 26% [17, 19, 20]. This initial barrier to clinic presentation can be further compounded by centralization of TB testing at referral laboratories, which requires individuals to return to the clinic to get results, and in some cases, a third time to initiate treatment. Furthermore, though the median time study staff spent conducting in-home testing was longer than in SoC households, median wait times accessing services in South African primary health clinics, including TB testing, have been reported well in excess of the time spent performing in-home testing [39, 40]. Our study found that in-home testing increased the proportion of symptomatic individuals tested for TB and significantly decreased the time from screening to receiving of test results, thus streamlining progression along the TB testing cascade. This underscores the potentially profound impact of in-home point-of-care testing in overcoming barriers to TB testing and reducing the time to accessing testing services and receiving a test result. This reduction in time to receiving a test result may be crucial in minimizing the overall patient-level financial burden and time-to-treatment initiation, thereby potentially mitigating household costs and the duration of transmission.

Our study had several limitations. First, although we found differences between study arms at different steps of the testing cascade, our sample size was limited because of the pilot nature of this study. In a similar vein, reaching any conclusions regarding the sensitivity of home-based testing to detect TB given the equal number of TB cases identified per study arm would be scientifically and statistically inappropriate. A properly powered study must be conducted to determine the true effect size of in-home testing on the TB testing cascade, case detection, and the generalizability of these results. Despite this limitation, our confidence in the acceptability of in-home TB testing by HHCs is reinforced through triangulation with qualitative data from these same HHCs [22]. Second, although this study was conducted in a high HIV prevalence setting, because in-home TB testing had never been done before, we refrained from also offering an HIV test because we would not be able to discern if nonparticipation was due to refusal to test for HIV, acceptability of in-home TB testing, or a compounding of TB- and HIV-related stigmas. Third, our study did not include any cost-effectiveness analysis or evaluation of the impact of constant transport or environmental changes on the long-term operability of the GeneXpert device. Future studies must include such components to ensure robust assessments of the true feasibility of home-based testing as a viable active case finding intervention. Finally, we only tested HHCs that reported TB-related symptoms. Given the estimated large pool of subclinical TB in South Africa [41], although techniques such as sputum induction can facilitate the production of quality spot sputum, future studies may benefit from collecting oral swab specimens in conjunction with sputum [42].

CONCLUSION

In-home point-of-care testing to diagnose TB is acceptable and feasible. By substantially increasing access to testing, it may also drastically improve early case detection compared to current active case finding approaches. Furthermore, in-home testing may also reduce the time to receiving test results and decrease time-to-treatment initiation.

Notes

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Data Sharing. All data and accompanying code book are freely available at Open Science Framework (OSF) under project name *Acceptability and Feasibility of Home-based TB Testing* (URL: https://osf.io/eywtc/; Identifier: DOI 10.17605/OSF.IO/EYWTC).

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Potential conflicts of interest. The authors: No reported conflicts of interest.

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