E-ISSN: 2706-9575
P-ISSN: 2706-9567
IJARM 2021; 3(2): 644-649
Received: 09-09-2021
Accepted: 13-10-2021

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Production from facilities targeted Xpert and mycobacterial culture testing for TB in high-risk groups visiting primary care centers

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DOI: https://doi.org/10.22271/27069567.2021.v3.i2i.463

Abstract
Background: We report the yield of targeted universal tuberculosis (TB) testing of clinic attendees in high-risk groups.
Methods: Clinic attendees in primary healthcare facilities in India with one of the following risk factors underwent sputum testing for TB: living with human immunodeficiency virus (HIV), contact with a TB patient in the past year, and having had TB in the past 2 years. A single sample was collected for Xpert-Ultra (Xpert) and culture. We report the proportion positive for Mycobacterium tuberculosis. Data were analyzed descriptively. The unadjusted clinical and demographic factors' relative risk of TB detected by culture or Xpert were calculated and concordance between Xpert and culture is described.
Results: A total of 30 513 participants had a TB test result. Median age was 39 years, and 11 553 (38%) were men. The majority (n=21734, 71%) were living with HIV, 12 492 (41%) reported close contact with a TB patient, and 1573 (5%) reported prior TB. Overall, 8.3% were positive for M. tuberculosis by culture and/or Xpert compared with 6.0% with trace-positive results excluded. In asymptomatic participants, the yield was 6.7% and 10.1% in symptomatic participants (with trace-positives excluded). Only 10% of trace-positive results were culture-positive. We found that 55% of clinic attendees with a sputum result positive for M. tuberculosis did not have a positive TB symptom screen.
Conclusions: A high proportion of clinic attendees with specific risk factors (HIV, close TB contact, history of TB) test positive for M. tuberculosis when universal testing is implemented.

Keywords: Tuberculosis, active case-finding, Xpert, subclinical tuberculosis

Introduction
The World Health Organization (WHO) estimates that 40% of people with active tuberculosis (TB), more than 4 million people, are not diagnosed or started on TB treatment [1]. Dubbed the "missing cases," identifying and treating this group are central to the WHO End TB Strategy [2]. South Africa, with the second highest annual incidence of TB in the world [1], has an estimated 150 000 cases of untreated TB per year, accounting for 40% of the country's total TB burden [3, 4]. Global TB control strategies have focused primarily on passive identification of symptomatic individuals who present to healthcare facilities. However, this symptom-directed approach is inadequate for detecting the majority of people with TB [5-7]. The WHO 4-question symptom screen (cough, fever, weight loss, and night sweats) misses up to half the TB cases among people living with human immunodeficiency virus (HIV) on antiretroviral therapy (ART) [8] and 70% of pregnant women living with HIV and TB [9-11]. These cases are missed due to both the poor reliability of symptom screening in facilities [12-14] and to a subset of people with subclinical TB (ie, people who have no symptoms or minimal symptoms). Targeted Universal Testing for TB (TUTT) was a cluster randomized trial that compared standard-of-care symptom-directed testing for pulmonary TB to universal testing in high-risk groups in 62 primary healthcare clinics in India. In TUTT, we targeted clinic attendees with HIV, those who self-reported close contact with a TB patient, and those with a history of TB in the preceding 2 years. The main findings of the TUTT trial have been reported elsewhere. In this study, we report on the yield of testing and the performance of Xpert-Ultra Mycobacterium tuberculosis/rifampin (Xpert) relative to liquid culture in each of the 3 high-risk groups in the TUTT intervention arm.

Methods

Setting and Study Design

Sixty-two clinics in India (Andhra Pradesh, Telangana, and Tamil Nādu) were selected for randomization in the trial if they diagnosed an average of ≥10 patients/month with TB. Three additional facilities were added to the intervention arm post hoc due to facility closures or other competing research in the same facilities. The 33 intervention clinics are included in this analysis.

Study Procedures

The intervention period was from March 2020 to March 2021 and halted 1 month prior to the planned study end date due to the India coronavirus disease 2020 lockdown. Study team members introduced the study to clinic attendees in waiting areas, inviting them to participate. Additionally, clinic nurses informed potential participants of the study. Eligible participants provided written informed consent. A brief questionnaire was used to elicit a standard WHO TB symptom screen with sociodemographic and clinical variables. We did not ask clinic attendees their reasons for clinic attendance. People attending the clinic for nonclinical reasons, including accompanying others or collecting medication, were eligible for participation. All participants were requested to provide 1 spot, spontaneously expectorated sputum. If unable to produce sputum, they were asked to give a forced cough effort, spit whatever was in their mouth, and repeat. Routine specimen transport was used to deliver specimens to the nearest public sector laboratory with mycobacterial culture capacity.

Laboratory Testing

Testing was performed at 4 public sector National Health Laboratory Service laboratories. Specimens were decontaminated with N-acetyl-L-cystine and sodium hydroxide and then centrifuged. The resulting pellet was resuspended and split for Xpert (Cepheid, Sunnyvale, CA) and for liquid mycobacterial culture testing using the Mycobacterial Growth Indicator Tube (MGIT) automated BancTec 960 instruments (Becton Dickinson, Franklin Lakes, NJ). Species identification of culture-positive specimens was performed using 1 of the following: MPT64 antigen, Genotype MTBDRplus, or GenoType Mycobacterium CM line probe assays (Hain Lifesciences, Germany). Results of microbiological tests were made available to clinics through routine reporting systems. Positive results for M. tuberculosis were also sent to study staff who notified clinics.

Classification of Xpert Results

Xpert results were categorized as positive for M. tuberculosis, negative, or trace. Trace is a semiquantitative category that corresponds to the detection of a very low bacillary load. Because of concerns regarding the specificity of Xpert trace results, the interpretation varies according to the clinical scenario. In India, the guideline is to await confirmatory TB culture prior to treatment except in people with HIV and no prior history of TB in whom Xpert trace results are sufficient for treatment. We classified Xpert results as follows: total positive, including trace, all results where M. tuberculosis was detected by Xpert, including trace-positive; trace reclassified, Xpert reclassified as TB-negative in participants with a prior history of TB; and trace excluded, all trace-positive Xpert results were reclassified as TB-negative.

Data Analysis

Participants were excluded from the yield analysis if they did not produce a specimen, testing was not performed due to specimen loss or leak, or there was culture contamination or growth of nontuberculous mycobacteria. Descriptive statistics are presented using counts, proportions, and medians with interquartile ranges (IQRs). We further stratified results by province, self-reported TB symptoms, CD4 count, and HIV treatment status. We report the number needed to be tested (NNT) to identify 1 person with a positive test for M. tuberculosis. In those participants whose specimen provided both Xpert and culture results, we report concordance between the 2 assays. Participants with more than 1 targeted risk factor were included in each of their group analyses. We used log binomial regression and adjusted for clustering by clinic to calculate the relative risk (RR) of having a positive TB test by patient and clinical characteristics.

Results

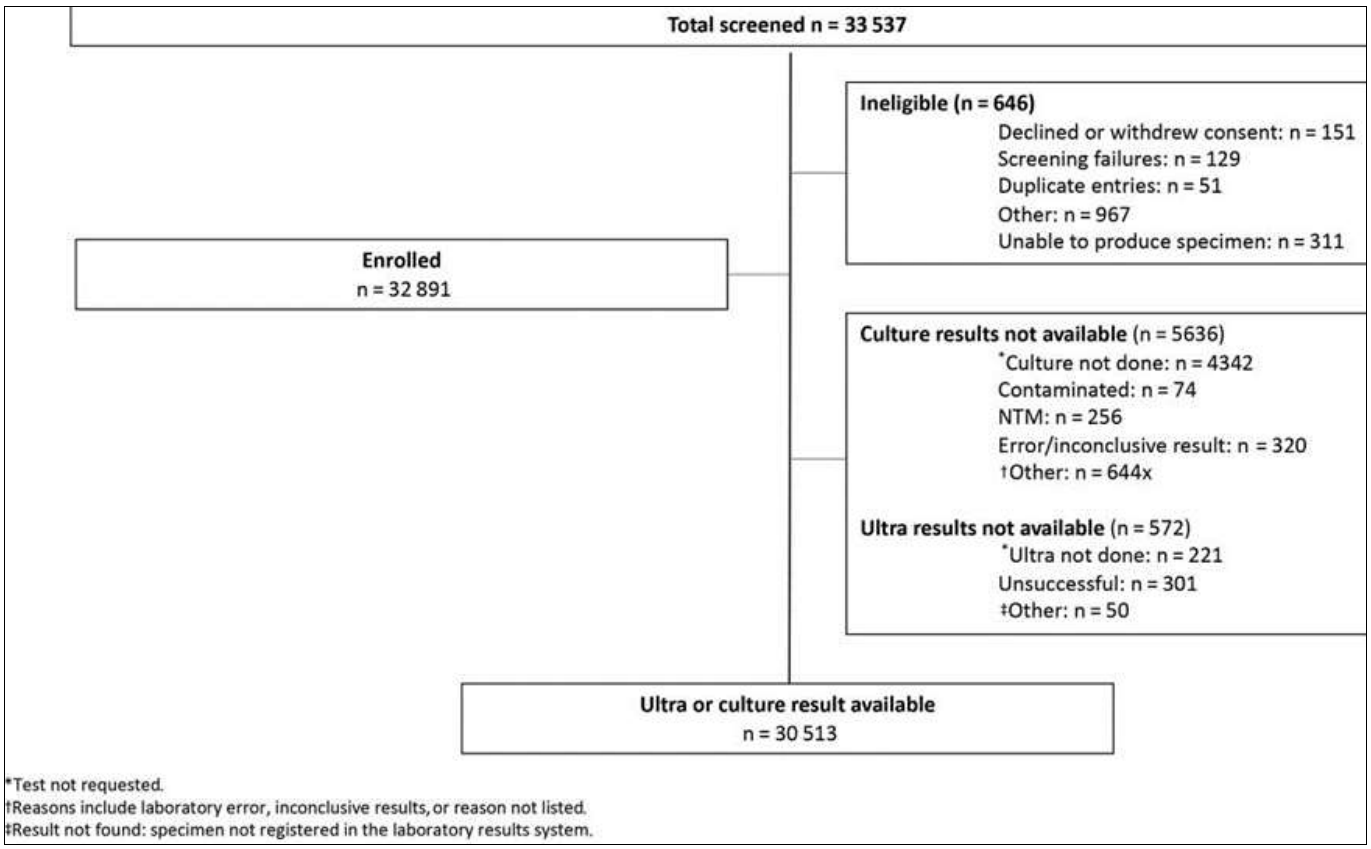
Participant Characteristics

A total of 33 537 participants were screened and consented, and 646 were ineligible (Figure 1). Of the 32 891 enrolled participants, 30 513 (93%) had either or both an Xpert or MGIT result available and were included in this analysis. The median age was 39 years (IQR, 30–46), and 38% of participants were men (Table 1). Of the 3 targeted risk factors, 71% (n=21 734 of 30 510) of participants were living with HIV, 41% (n=12 492 of 30 496) reported a recent close contact with a TB patient, and 5% (n=1573 of 30 476) had TB in the preceding 2 years (Figure 2). Among participants with HIV in whom ART treatment status was recorded (n=8510), 87% reported being on ART, and the median duration on treatment was 3.2 years (IQR, 1.1–6.0). The most recent CD4 count was recorded in 40% of study participants with HIV. The median CD4 value was 422 cells/mm3 (IQR, 248–613). Overall, 27% (95% confidence interval [CI]: 26%–27%) of participants reported at least 1 TB symptom (cough, loss of weight, fever or night sweats). Supplementary Table 1 provides a description of participant characteristics with nonoverlapping risk factors (living with HIV, prior TB and not living with HIV, and household contact without HIV or prior TB).

Yield by Risk Factor

Overall, 8.3% (95% CI: 7.9%–8.6%) of participants had a positive test for M. tuberculosis by culture and/or Xpert; 8.1% (95% CI: 7.8%–8.4%) with trace-positive results were reclassified as negative in those with prior TB and 6.0% with trace-positives excluded (95% CI: 5.7%–6.2%; Table 2A, Figure 3). The overall yield in people with HIV was 7.4% (95% CI: 7.1%–7.8%), 7.2% (95% CI: 6.9%–7.6%) and 5.0% (95% CI: 4.7%–5.3%) with trace-positive results reclassified and with trace-positive results excluded, respectively. Similarly, among people with a close TB contact, yield was 9.8% overall (95% CI: 9.2%–10.3%), 9.6% (95% CI: 9.1%–10.2%) and 7.5% (95% CI: 7.0%–8.0%) with trace-positive results reclassified and with trace-positive results excluded, respectively. The highest yield was among participants with a prior history of TB in the preceding 2 years: 16.3% overall (95% CI: 14.5%–18.2%)

and 12.0% with Xpert trace-positives excluded (95% CI: 10.3%–13.6%). The overall NNT to obtain 1 positive test using culture and Xpert was 12, with all Xpert-positive results inclusive of trace and 17 with trace-positive results excluded. Similarly, in individuals living with HIV, NNT were 13 and 20, respectively; in those with a TB contact, NNT was 10 and 13, respectively; and in the group with prior TB, NTT was 6 and 8, respectively.



Yield in Participants Based on Reported Symptom Status

Overall, of participants with a positive TB test (MGIT- and/or Xpert-positive, trace excluded), only 45% (826 of 1820) reported at least 1 symptom of TB. Among participants who were WHO symptom screen–negative, the yield was 6.7% (95% CI: 6.4%– 7.0%) by Xpert and/or culture and 6.5% (95% CI: 6.3%–6.9%) with trace-positive results reclassified as negative in those with prior TB and 4.5% (95% CI: 4.2%–4.7%) with trace-positive results excluded. The overall asymptomatic NNT was 22 vs 15; 27 vs 17 in people with HIV; 17 vs 12 in TB contacts; and 10 vs 7 in those with a prior history of TB depending on the inclusion of trace results. The yield in symptomatic participants is described in Supplementary. However, there was significant variability in the frequency of symptom screen positivity by interviewer, ranging from 0% to 85% (median, 27%; IQR, 5%–52%; Supplementary Figure 2). Furthermore, in the first 3 months of the study (May 2019–July 2019), a much higher proportion of interviewers reported symptom positivity among participants (median symptom positivity rate, 57% per interviewer [IQR, 42%–72%] vs in the last 3 months of the study (January 2020–March 2020; median, 3% symptom positivity; IQR, 0.5%–22%).

Variability in Yield by Province and Facility

The yield of testing varied considerably between provinces and facilities. The yield was 2.0% (95% CI: 1.7%–2.4%) in Andhra pradesh, 7.1% (95% CI: 6.5%–7.6%) in Telangana, and 7.0% (95% CI: 6.5%–7.5%) in the Tamil Nadu (trace-positives excluded). Moreover, individual clinics had markedly different yields within the same province (Supplementary).

Yield in HIV by ART Status, CD4 Strata, and Presence of Reported Symptoms

In participants with HIV on ART, 4.0% (95% CI: 3.5%–4.4%) were positive for M. tuberculosis (trace-positives excluded; Supplementary Figure 1A), whereas in those not on ART, 12.2% (95% CI: 10.4%–14.1%) had a positive test. The yield was highest (5.1%; 95% CI: 4.0%–6.3%) in those with CD4 500 cells/mm3 (Supplementary Figure 1B). Most people with HIV and a positive test for M. tuberculosis did not report TB symptoms; only 19% (n = 57 of 293; 95% CI: 15%–24%) of people on ART with TB and 39% (n = 51 of 130; 95% CI: 31%–48%) of those not on ART with TB reported at least 1 symptom of TB.

Table 1: Demographic and Clinical Characteristics of Study Participants Enrolled at Intervention Clinics of a Cluster Randomized Trial of Targeted Universal Testing for Tuberculosis in High-Risk Groups

Characteristic	Entire Cohort[a] (n = 30 513)	HIV[a] (n = 21 734)	TB Contact[a] (n = 12 492)	Prior TB[a] (n = 1573)
Age, median (IQR), y	39 (30–46)	39 (31–46)	39 (27–49)	40 (30–48)
Gender, no. (%)				
Missing	26 (0)	15 (0)	15 (0)	3 (0)
Female	18 934 (62)	14 124 (65)	7359 (59)	757 (48)
Male	11 553 (38)	7595 (35)	5118 (41)	813 (52)
Symptom status, no. (%)				
Missing	41 (0)	36 (0)	7 (0)	3 (0)
Asymptomatic	22 255 (73)	16 970 (78)	7796 (62)	868 (55)
Symptomatic	8217 (27)	4728 (22)	4689 (38)	702 (45)
Human immunodeficiency virus status, no. (%)				
Missing	587 (2)	…	568 (5)	41 (2)
Negative	8192 (29)	…	7905 (63)	531 (34)
Positive	21 734 (71)	…	4019 (32)	1001 (64)
CD4 count available,[b] no. (%)	8700 (40)	…	1618 (40)	489 (49)
CD4 count, median (IQR), cells/mm^3	422 (248–613)	…	472 (298–674)	294 (147–523)
ART status known[b]	8510/21 734 (39%)	…	1529/4019 (38%)	327/1001 (33%)
On ART at enrollment (%)	7421/8510 (87%)	…	1132/1529 (74%)	279/327 (85%)
TB contact, no. (%)				
Missing	17 (0)	15 (0)	…	4 (0)
No	18 004 (59)	17 700 (81)	…	1076 (68)
Yes	12 492 (41)	4019 (19)	…	493 (31)
Prior TB, no. (%)				
Missing	37 (0)	25 (0)	12 (0)	…
No	28 903 (95)	20 708 (95)	11 987 (96)	…
Yes	1573 (5)	1001 (5)	493 (4)	…
Completed treatment	599 (38)	…	…	…
Long-term follow-up	38 (2)	…	…	…
Outcome unknown	936 (60)	…	…	…
Time since TB treatment stopped, no. (%)				
Missing	68 (4)	…	…	…
<1 y	505 (32)	…	…	…
1–2 y	484 (31)	…	…	…
2–5 y	448 (28)	…	…	…
>5 y	68 (4)	…	…	…
Province				
Andhra Pradesh, no. (%)	6593 (22)	5816 (27)	877 (7)	111 (7)
Telangana, no. (%)	14 381 (47)	9480 (44)	7586 (61)	1007 (64)
Tamil Nadu, no. (%)	9539 (31)	6438 (30)	4029 (32)	455 (29)

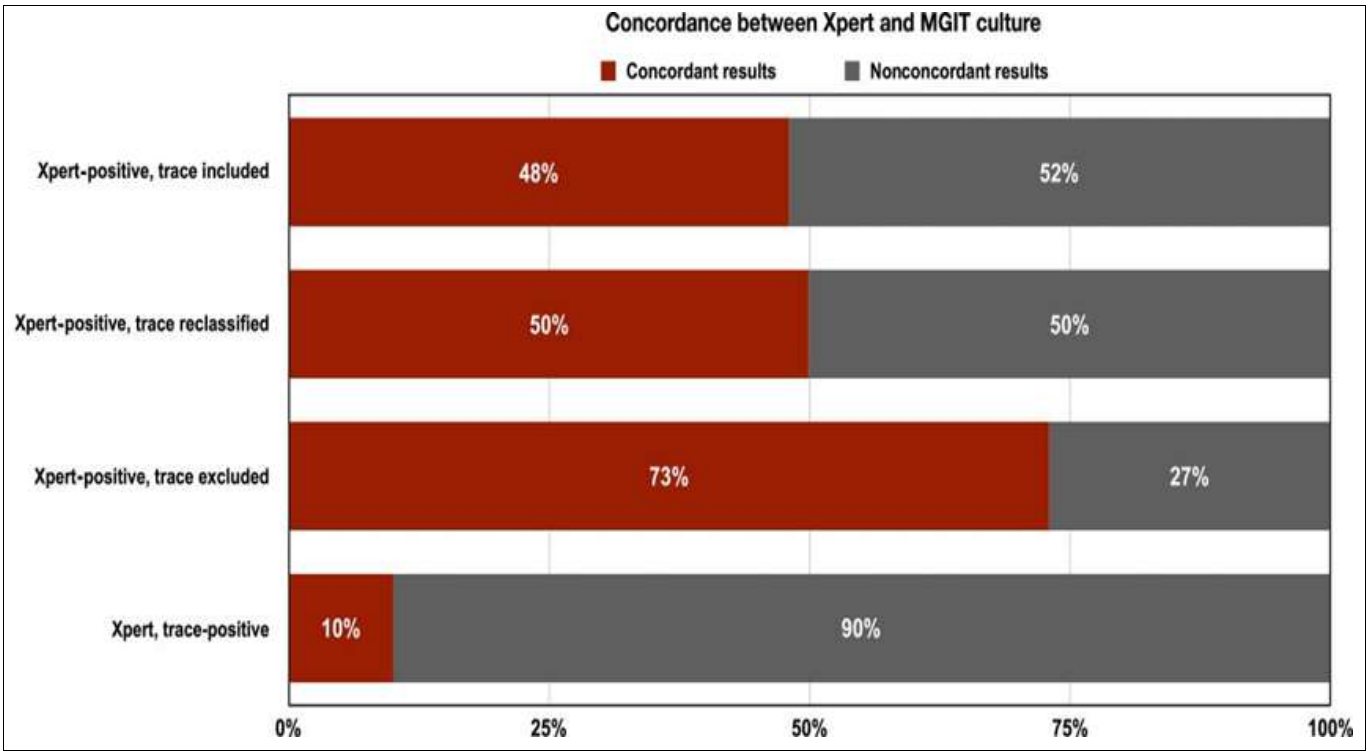
Abbreviations: ART, antiretroviral therapy; HIV, human immunodeficiency virus; IQR, interquartile range; TB, tuberculosis. a
Note that the row totals and percentages do not total 100% in all cases as the risk factor groups are not mutually exclusive.
b the protocol was amended to include these questions partway through the study, and these data points were collected after recruitment was underway

Discussion

Our study shows that the yield of universal testing for pulmnary TB in clinic attendees at high risk of TB is high when all are requested to provide a sputum specimen, irrespective of the outcome of symptom screening. Indeed, in this study, between 6% and 8% had an Xpert or culture result positive for M. tuberculosis depending on the interpretation of trace positive results. We further show that the yield of testing was high even in those in whom no history of TB symptoms was elicited; 4.5% had a positive test for M. tuberculosis. Additionally, Xpert had poor concordance with MGIT liquid culture in this population, with only half of all Xpert-positive results being culture positive. Finally, there was substantial regional and facility variability in the yield of testing, ranging from 1% to 13%, suggesting that additional targeting by province and clinic could further refine the targeted testing strategy we report here. Although the yield was much higher in people who reported 1 or more TB symptoms in the WHO symptom screen, a substantial proportion of bacteriologically confirmed cases would be missed by ignoring high-risk groups in whom symptoms are not elicited by healthcare providers. Overall, no history of TB symptoms was elicited in 55% of the positive TB cases in this study.

Among people with HIV, our finding that 3.7% of clinic attendees had TB but did not report TB symptoms is consistent with prior data from the region [15]. The proportion of positive TB cases who were symptom screen–negative was higher among those on ART than those not on ART, which is also consistent with findings from a large meta-analysis of the sensitivity of the WHO symptom screen in people living with HIV [8]. It remains unknown if these participants were truly asymptomatic or if this was the result of the poor reliability of symptom screening. The variability in positive symptom screen rates among interviewers and across the duration of the trial suggests that symptom screening was not consistently administered. This lends further support that high-quality, consistent TB

symptom screening is challenging to implement at scale [12–14] and that no symptom-based screening approaches are required to identify TB in high-risk groups in healthcare facilities. Of the 3 targeted risk groups, the yield of testing was highest among those with a prior history of TB; 12% had detectable TB, supporting calls for intensive follow-up of people who recently completed TB treatment. However, they represented a small fraction (5%) of all participants in this study and only 10% of all diagnosed TB cases, making this a challenging population to identify in primary healthcare settings. The high rate of HIV coinfection in this group (64%) suggests that most of the TB cases could have been identified by targeting people within the HIV treatment program. Although there was a 3-fold higher risk of TB in those not on ART compared with those who initiated ART, 75% of TB cases occurred in people on ART, suggesting that a focus of universal TB testing on adults not yet on ART would miss most of the prevalent TB in this risk group. Last, our data demonstrate that the targeted testing of TB contacts attending clinics could offer a potentially cost-effective alternative to community and homebased screening of TB contacts as the numbers of TB contacts were readily identified in study clinics. We found that male clinic attendees were more than twice as likely to have TB than female clinic attendees, which accords with the epidemiology of TB in sub-Saharan Africa [3]. The lower participation of men in our study mirrors the lower engagement of men in primary healthcare and HIV services in the region. However, this study demonstrates that a clinic-based intervention can be an effective option for finding prevalent TB in men. The most concerning finding of our study was the poor concordance between Xpert and culture. Crucially, this finding was not limited to trace-positive results. In our study, only 48% of Xpert-positive results were culture-positive. Moreover, this only improved to 73% when trace-positive results were excluded (only 10% of trace-positive results were MGIT-positive). This is comparable to the rate of concordance between Xpert and culture seen in other studies where people were tested irrespective of symptoms (eg, prevalence surveys; high-risk groups such as miners, people with HIV, household contacts). Most notably, in the South African National Prevalence Survey in which people were tested on the basis of symptoms or an abnormal chest X-ray, only 65% of positive Xpert results (including trace) were culture-positive. These findings contrast with the performance of Xpert in presumptive TB cases (ie, people with symptoms), where 90% of positive Xpert results and 30%–50% of trace-positive results were culture-positive. There are multiple possible explanations for the low Xpert vs culture concordance we report. First, MGIT is an imperfect gold standard and may miss some true-positive cases. Also, by splitting specimens and decreasing the mycobacterial burden in each sample, the sensitivity of culture for detecting TB may have been reduced and contributed to the elevated rate of discordance seen in this study. Furthermore, we know that Xpert can be positive in people with prior treated TB who have mycobacterial DNA but no replicating bacteria, and our study population was enriched for people with prior TB. Given that the reported rate of prior TB in people with HIV ranges from 8% to 25% in the region [15], this is going to be a significant challenge to implementation of universal testing for TB using Xpert in people with HIV in ART facilities. Further work to evaluate this population prospectively with serial sampling, chest imaging, and longitudinal follow-up is critical to understanding the clinical implications of molecular test–positive, culture-negative results, especially in people with no prior history of TB. It is not known if this is a group at risk of progression to clinical TB disease, whether treatment is indicated, and if they pose a transmission risk



Conclusions

Our results indicate that case detection strategies based on routine symptom screening of clinic attendees do not identify all adults with pulmonary TB. The targeted universal testing approach described in this study has a high yield for M. tuberculosis and should be part of an expanded testing strategy, although costs and laboratory capacity need to be assessed as barriers to implementation. The high prevalence of pulmonary TB in patients attending primary healthcare clinics presents an important opportunity for early detection of TB that may diminish transmission and also prevent future TB-related morbidity and mortality.

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