

Prevalence of Mycobacterium tuberculosis in sputum and reported symptoms among clinic attendees compared to a community survey in rural South Africa

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Summary: *In primary healthcare facilities and the surrounding community in rural South Africa, most people with Mycobacterium tuberculosis in sputum reported no symptoms. TB case finding restricted to symptom screening in health facilities will miss many people with active disease.*

ABSTRACT

Background:

Tuberculosis (TB) case finding efforts typically target symptomatic people attending health facilities. We compared the prevalence of *Mycobacterium tuberculosis* (*Mtb*) sputum culture-positivity among adult clinic attendees in rural South Africa with a concurrent, community-based estimate from the surrounding demographic surveillance area (DSA).

Methods:

Clinic: Randomly-selected adults (≥ 18 years) attending two primary healthcare clinics were interviewed and requested to give sputum for mycobacterial culture. HIV and antiretroviral therapy (ART) status were based on self-report and record review. Community: All adult (≥ 15 years) DSA residents were invited to a mobile clinic for health screening, including serological HIV testing; those with ≥ 1 TB symptom (cough, weight loss, night sweats, fever) or abnormal chest radiograph were asked for sputum.

Results:

Clinic: 2,055 patients were enrolled (76.9% female, median age 36 years); 1,479 (72.0%) were classified HIV-positive (98.9% on ART) and 131 (6.4%) reported ≥ 1 TB symptom. Of 20/2,055 (1.0% [95% CI 0.6–1.5]) with *Mtb* culture-positive sputum, 14 (70%) reported no symptoms. Community: 10,320 residents were enrolled (68.3% female, median age 38 years); 3,105 (30.3%) tested HIV-positive (87.4% on ART) and 1,091 (10.6%) reported ≥ 1 TB symptom. Of 58/10,320 (0.6% [95% CI 0.4–0.7]) with *Mtb* culture-positive sputum, 45 (77.6%) reported no symptoms.

In both surveys, sputum culture positivity was associated with male sex and reporting >1 TB symptom.

Conclusions:

In both clinic and community settings, most participants with *Mtb* culture-positive sputum were asymptomatic. TB screening based only on symptoms will miss many people with active disease in both settings.

Keywords: *Tuberculosis; sputum; culture-positive; prevalence; South Africa*

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INTRODUCTION

South Africa is a high tuberculosis (TB) burden country with an HIV-driven epidemic [1]. The most recent estimated incidence rate is approximately 615 per 100,000 per year; 58% of all people with TB are living with HIV [2]. While increased access to antiretroviral therapy (ART) has contributed to improved TB prevention and care, TB remains the leading cause of death in South Africa [3,4]. TB case finding policy in most high-TB prevalence settings recommends routine symptom screening of all adult clinic attendees and testing those who self-present with TB symptoms (cough of any duration, night sweats, loss of weight, or fever)[5,6]. However, difficulties with facility-based case finding result in delays and missed opportunities for case detection [7-10].

Despite broad access to Xpert® MTB/RIF and more recently Xpert® MTB/RIF Ultra, the national TB prevalence in South Africa was estimated to be 737 per 100,000 in 2018 [11]. Given the impact of the coronavirus disease 2019 (COVID-19) pandemic on TB detection, there is a clear need for earlier identification and treatment of people with active TB [2,12]. We conducted a survey at two primary healthcare clinics (PHC) clinics in KwaZulu-Natal, South Africa, within the Africa Health Research Institute (AHRI) demographic surveillance area (DSA)[13], to estimate the prevalence of *Mycobacterium tuberculosis* (*Mtb*) culture-positive sputum among adult clinic attendees. During the same period, a population-wide, community-based survey was being conducted in the DSA that included screening and testing adults for TB [14]. In this analysis we compared the prevalence of sputum culture-positivity between individuals attending clinics for ambulatory care and individuals in the surrounding community.

METHODS

Ethics statement

The ethics committees of the University of KwaZulu-Natal and the London School of Hygiene & Tropical Medicine granted approval for both surveys. Partners Human Research Committee Institutional Review Board of Partners HealthCare in the United States of America approved the community-based survey. Data linkage was conducted under ethics approval for the AHRI DSA [13].

All enrolled participants gave written consent or witnessed verbal consent for those who could not read or write.

Study Design

Clinic Survey

In a cross-sectional study between June 2018 and May 2019, adults (aged ≥ 18 years) attending for healthcare were randomly selected from two PHC clinics in Hlabisa sub-district of uMkhanyakude, using AHRI's electronic patient registration system as a sampling frame [15]. Exclusion criteria included attending for an emergency visit, being in labour, previous participation in the survey, or attending on behalf of a patient. Consenting adults completed a questionnaire focused on their reason for clinic attendance, TB history, and presence or absence of TB symptoms (as defined above), or any other symptoms (as an open question). Mid-upper arm circumference (MUAC) was measured, with a < 24 cm cut-off as a proxy indicator of low body mass index (BMI) [16]. Participants confidentially recorded their HIV and ART status on the digital tablet provided. All participants were asked to produce a single sputum specimen, which was sent to the AHRI Research Diagnostic Laboratory for culture in liquid media using the Mycobacteria Growth Indicator Tube system (MGIT; [Becton Dickinson Microbiology Systems, USA]) and phenotypic drug sensitivity testing (DST) using

the solid agar 1% proportion method for *Mtb* complex. Any participant who reported having ≥ 1 TB symptom was asked to provide a second sputum specimen for testing in the public health system using Xpert® MTB/RIF Ultra (Xpert Ultra; [Cepheid, USA]). Participants' clinic files were reviewed for evidence of HIV and TB testing and treatment within the 12-week period after enrolment. Additional details on the survey design, participant selection and laboratory procedures are provided in supplemental methods.

Community Survey

During the baseline data collection period, 36,097 AHRI DSA resident adults (aged ≥ 15 years) were eligible for enrolment. Individuals were invited to participate in a mobile screening and multi-disease testing camp that moved through the study area [14]. We report on participants who enrolled in the first 12 months of the community survey, contemporaneous with the clinic survey. As part of a comprehensive health and treatment history, all enrolled participants were screened for TB symptoms, had a MUAC measurement taken and, unless pregnant, a digital chest radiograph, which was analysed using version 5 of the computer-aided detection for TB (CAD4TB; [©Thirona, Netherlands]) software. Participants who reported ≥ 1 TB symptom, had a CAD4TB score of >60 (between May to September 2018) or >25 (from October 2018 onwards), or were pregnant were asked to produce sputum. The sputum specimen was divided into two in the AHRI laboratory: one portion was tested using Xpert Ultra and the other was cultured on MGIT. Positive cultures underwent first-line DST. All participants had blood drawn for HIV testing (Genscreen Ultra HIV Ag-Ab enzyme immunoassay [Bio-Rad]). Participants with a positive HIV immunoassay had a reflex HIV-1 RNA viral load performed (**Abbott RealTime HIV-1 Viral Load [Abbott, USA]**).

In both studies, participants' results were reviewed by a study clinician and participants were contacted and referred to care and treatment as appropriate.

Study outcomes

The primary outcome for this analysis was a sputum positive for *Mtb* on liquid culture. Participants who were unable to produce a sputum specimen were considered sputum culture-negative. Only *Mtb* culture-positive cases from the community survey were compared to those in the clinic survey. A secondary analysis including Xpert Ultra results is described further in supplemental methods and HIV/ART status in Table S1.

Data management and statistical considerations

Data were captured electronically using Research Electronic Data Capture (REDCap®) tools (Vanderbilt University, USA) hosted at AHRI. Data entry for both studies was done using encrypted Android tablets. Data were analysed using Stata/IC 15.1 (Stata Corporation, USA) and R 3.5.0 [20].

The sample size for the clinic survey was based on a precision estimate, assuming the prevalence of TB in the general population was 1.5% [21], and among PHC clinic attendees to be around 3%. To allow for estimation of an overall TB prevalence of 3% with a precision of $\pm 0.8\%$, the study aimed to enrol 3,400 adult attendees (1,700 per clinic) to obtain the target sample size of 2,000 participants with a sputum sample, assuming that 60% could produce a specimen. No formal sample size calculations were done for the community survey, since all resident adults were eligible to participate. However, the first 10,000 participants permitted estimation of a prevalence of *Mtb*-positive sputum of 1% with a precision of $\pm 0.2\%$.

The prevalence of culture-confirmed *Mtb* and its 95% confidence interval (CI) were calculated for each survey. Supplemental methods describe the sensitivity analysis, data linkage for the clinic survey, and risk factor analysis for both surveys.

RESULTS

Clinic Survey

Between 25 June 2018 and 21 May 2019, 3,506 of 7,333 patients were electronically sampled and 243 were manually sampled, giving a total 3,749 patients. Following screening and consent procedures, 2,055 participants were enrolled into the study (Figure 1), fewer than originally intended because the study started later than planned Figure S1 illustrates the full enrolment cascade. Table S2 compares characteristics of participants and non-participants among those sampled and eligible to participate, based on data linkage methods.

Among the 2,055 participants enrolled, median age was 36 (interquartile range [IQR] 28–48) years and 76.9% were female (Table 2). 1,479 (72%) participants were classified as HIV-positive, of whom 1,463 (98.9%) were taking ART. 1,189 (80%) of those classified as HIV-positive reported visiting the clinic for HIV care on the day of enrolment. 505/2,055 (24.6%) participants reported past TB treatment, 14/2,055 (0.7%) reported current TB treatment and 131/2,055 (6.4%) reported having ≥ 1 TB symptom at enrolment.

1,035/2,055 (50.4%) participants produced a sputum specimen, of which 47 were contaminated; 988 specimens were included in analysis. 20 participants gave a sputum specimen that grew *Mtb*, giving a prevalence of 1.0% (95% CI 0.6–1.5; 973 [95% CI 630–1,050] per 100,000; Figure 1), which was not substantially altered (1.0% [95% CI 0.6–1.5]; 990 [95% CI 640–1,054] per 100,000) after adjusting for non-response (Table S4).

Among the 20 participants with a positive *Mtb* sputum culture, median age was 37 years and nine (45.0%) were male (Table 2). 13/20 (60.0%) reported having no history of TB, 15/20 (75.0%) were classified as HIV-positive (all on ART), and 6/20 (30.0%) reported having ≥ 1 TB symptom. Four (25.0%) *Mtb* isolates were found to be multidrug-resistant (resistant to rifampicin and isoniazid) and

one (5.0%) mono-resistant to rifampicin. Three (60.0%) out of 5 sputum specimens with drug resistant isolates were collected from participants who reported being previously treated for TB. All 20 participants with culture-positive sputum had further sputum tests at varying time points over the course of their care in the public health service, of which 12 were positive (Table S5).

Community survey

Between 24 May 2018 and 25 May 2019, research teams visited 3,195 households in the DSA and attempted to contact 19,157 individuals, 15,234 of whom were successfully contacted and invited to participate in the community survey (Figure 1). Of these, 578 declined and a further 4,336 did not attend the mobile camps, leaving a total 10,320 enrolled participants. Of these, 6,481 were asked to give a sputum specimen based on reporting one or more TB symptoms ($n = 1,091$), having a CAD score above the study threshold ($n = 5,491$) or being pregnant ($n = 328$; Table S3).

Among the 10,320 enrolled participants, the median age was 38 years, 68.3% were female, 3,105 tested HIV-positive, and 2,714 (87.4%) were on ART (Table S3). 1,228/10,320 (11.9%) reported past TB treatment, 45/10,320 (0.4%) reported current TB treatment and 1,091/10,320 (10.6%) reported having ≥ 1 TB symptom at enrolment. 5,274/10,320 produced sputum specimens, of which 420 were contaminated, leaving 4,854 included in the analysis. 58 sputum specimens cultured *Mtb* on liquid media giving a prevalence of 0.6% (95% CI 0.4–0.7; 562 [95% CI 420–710] per 100,000; Figure 1) that remained the same after adjusting for non-response (0.6% [95% CI 0.4–0.7]; 562 [95% CI 430–740] per 100,000). In addition, 20 participants had sputum specimens that were culture-negative but Xpert Ultra positive (greater than trace).

Of the 58 participants with a positive *Mtb* sputum culture, the median age was 48 years and 28 (48.0%) were male (Table 1). 48/58 (82.2%) reported having no history of TB, 26/58 (44.8%) were HIV-positive, and 21/26 (80.8%) were taking ART. Nine (15.5%) *Mtb* isolates were found to be multidrug-resistant and two (3.4%) were mono-resistant to rifampicin. Two (18%) out of 11 sputum

specimens with drug-resistant isolates were from participants who reported previous TB treatment. The median age in the Xpert Ultra positive only group was 53 years and 12 (60.0%) were male. 5/20 (20.0%) reported having no history of TB, 10/20 (50.0%) were HIV-positive, and 9/10 (90%) on ART. Rifampicin resistance was detected in two (10.0%) of these specimens, one of the two specimens was from a participant who reported previous treatment for TB.

The effects of including Xpert Ultra positive and trace-positive results on study outcomes are described in Supplemental results and Table S4.

Associations with *Mtb* culture positive sputum

In a univariable analysis of the clinic survey data (Table 3), *Mtb* sputum culture-positivity was associated with TB symptoms (odds ratio [OR] 8.6 [95% CI 3.0–24.6], $p < 0.001$ for >1 TB symptom vs. none; OR 3.0 [95% CI 0.4–23.0], $p = 0.299$ for one TB symptom vs. none), and male sex (OR 2.8 [95% CI 1.1–6.7], $p = 0.024$).

In the community survey (Table 4) male sex (OR 2.0 [95% CI 1.2–3.4], $p = 0.008$), age >44 years (vs. 15–24 years, OR 2.5 [95% CI 1.2–5.9], $p = 0.02$), being HIV-positive on ART (vs. HIV-negative, OR 1.9 [95% CI 1.1–3.2], $p = 0.024$), a MUAC of <24 cm (vs. ≥ 24 cm, OR 3.2 [95% CI 1.7–5.7], $p < 0.001$), and reporting >1 TB symptom (vs. none, OR 4.5 [95% CI 1.9–9.0], $p < 0.001$) were associated with sputum culture positivity; results were little changed after weighting for non-response. In a multivariable analysis (Table 4), male sex (OR 2.4 [95% CI 1.4–4.0], $p = 0.001$), age >44 years (vs. 15–24 years, OR 2.7 [95% CI 1.3–6.3], $p = 0.016$) and being HIV-positive on ART (vs. HIV-negative, OR 2.0 [95% CI 1.1–3.5], $p = 0.022$) remained independently associated with sputum culture positivity.

DISCUSSION

We present simultaneous estimates of the prevalence of *Mtb* culture positive sputum among ambulatory clinic attendees and adults in the surrounding community. Based on culture results only, the prevalence among clinic attendees was slightly higher than in the community, and confidence intervals overlapped. In both surveys, most participants with culture-positive sputum did not report any symptoms, although reporting TB symptoms was associated with having culture-positive sputum. This has been reported in other community-based TB prevalence surveys [22-24], but not previously reported among adult clinic attendees. The degree of infectiousness of asymptomatic individuals with subclinical disease compared to symptomatic people is not known [25,26]. Symptom screening as the entry point to case detection in the current model of care needs to be revisited particularly if asymptomatic individuals are infectious.

In both surveys, the direction of the associations with risk factors was the same. HIV infection is a known risk factor for developing TB disease and, given the study setting, this finding is not unexpected [27]. HIV-positive people taking ART attend health facilities relatively frequently, giving more opportunities for TB screening, but screening limited to those attending for HIV care will miss HIV-positive patients who attend clinics for other reasons [28]. In addition, symptom-based screening for TB has lower sensitivity among people who are HIV positive and on ART [29].

TB prevalence estimates from previous studies based on exit interviews of only symptomatic adults attending PHC clinics in South Africa range between 3.6% [8] and 5% [9]. Our estimate of lower TB prevalence among clinic attendees in comparison to previous estimates is most likely a result of our attempt to construct a true random sample of adult ambulatory care attendees and request sputum from all those enrolled, regardless of symptoms.

Our community survey screening methods are comparable to other surveys [22,23,30,31], but our estimate is based on a single sputum specimen. National TB prevalence survey estimates are based on two specimens and our estimate is therefore likely to underestimate prevalence compared to the national survey and other surveys in which multiple samples are collected. Our community estimates are consistent with those reported in a recent study from Uganda based on a single sputum specimen tested with Xpert Ultra [24]. Including all Xpert Ultra positive tests resulted in an estimated community prevalence of 940 (95% CI 780–1,130) per 100,000, and 420 (95% CI 320–550) per 100,000 adults when Xpert Ultra trace-positive and culture negative sputum results were excluded.

Our community survey aimed to enrol as many DSA residents as possible; our sample was therefore not representative, but weighting for non-response did not materially affect our estimate. In both surveys, men were under-represented and may have resulted in an underestimate of overall prevalence, since men are known to be disproportionately affected by TB [32,33]. In the same way, our prevalence findings could be an overestimate if people who were ill were more likely to participate in the community survey, but this would not explain the high number of participants with culture-positive sputum who were asymptomatic at enrolment.

Chest radiography is the most sensitive TB screening method currently available [22,23,31,34] and has the potential to substantially increase the yield of case finding in high prevalence settings [35]. Although costly, digital chest radiography in combination with computer-aided detection software is a promising alternative in settings where limited human resources are a barrier to implementation [36].

Our analysis has the following limitations. Participation in both surveys was incomplete, but prevalence estimates were not substantially different after weighting for non-response. The clinic

survey did not achieve its intended sample size, resulting in a less precise estimate than planned. Only 50% clinic survey participants were able to produce a sputum sample, which may have resulted in an underestimate of the true prevalence of TB among clinic attendees. Because we did not request sputum from all participants in the community survey, we may have underestimated true prevalence. Due to logistical constraints, both surveys relied on a single sputum specimen from each participant to detect active TB, and our primary comparison is based on sputum MGIT culture only. Studies among patients being investigated for TB have estimated the incremental yield of culture-positive *Mtb* from a second sputum specimen to be between 6–10% [37,38]. In the clinic survey, most participants with culture-positive sputum had a second specimen confirming TB disease through routine care in the public health service. Had any of the clinic survey sputum specimens been false-positive cultures, our prevalence estimate would be an overestimate, in which case the true prevalence would be closer to the community-based estimate. In addition, because of the limited number of cases, false-positives could have biased the results of the multivariable analysis. Reliance on a single sputum specimen in the community survey could have resulted in an overestimate from false-positive results, but equally collecting only one specimen may have resulted in an underestimate of true prevalence [37].

In conclusion, TB case finding based on symptom screening and restricted to health facilities will miss many people with TB disease. If individuals without symptoms, in the subclinical phase of the disease, are infectious, the existing case finding strategy will need to be reconsidered. Work towards understanding the relative contribution of asymptomatic people to TB transmission is ongoing and will be of particular importance to determine the conditions under which symptom-agnostic screening algorithms should be considered. A clear strategy is also needed to detect HIV-negative people with TB in the community. There is an urgent need for better low cost, high sensitivity screening tests for TB in community and clinic settings.

NOTES

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Potential Conflicts

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REFERENCES

1. Churchyard GJ, Mametja LD, Mvusi L, et al. Tuberculosis control in South Africa: Successes, challenges and recommendations. *South African Med J.* 2014; 104: 244–8.
2. World Health Organization (WHO). *Global Tuberculosis Report 2020*. Geneva, Switzerland; 2020. Available at: <https://www.who.int/publications/i/item/9789240013131>. Accessed on 22 October 2020.
3. Tomita A, Smith CM, Lessells RJ, et al. Space-time clustering of recently-diagnosed tuberculosis and impact of ART scale-up: Evidence from an HIV hyper-endemic rural South African population. *Sci Rep.* 2019; 9: 1–9.
4. Loveday M, Mzobe YN, Pillay Y, Barron P, Sa F. Figures of the dead : A decade of tuberculosis mortality registrations in South Africa. *South African Med J.* 2019; 109: 728–32.
5. World Health Organization. *Systematic screening for active tuberculosis: Principles and recommendations*. World Health Organization. Geneva, Switzerland: WHO Press; 2013. Available at: https://www.who.int/tb/publications/Final_TB_Screening_guidelines.pdf. Accessed 27 July 2020.
6. South African National Department of Health. *National Tuberculosis Management Guidelines 2014*. Pretoria, South Africa; 2014. Available at: <https://www.knowledgehub.org.za/elibrary/national-tuberculosis-management-guidelines>. Accessed 27 July 2020.
7. Chihota V, Ginindza S, McCarthy K, Grant A, Churchyard G, Fielding K. Missed opportunities for TB investigation in primary care clinics in South Africa: experience from the XTEND trial. *PloS ONE.* 2015; 10: e0138149. Available from: <https://journals.plos.org/plosone/article/citation?id=10.1371/journal.pone.0138149>. Accessed on 27 July 2020.
8. Kweza PF, Schalkwyk C Van, Abraham N, Uys M, Claassens MM. Estimating the magnitude of pulmonary tuberculosis patients missed by primary health care clinics in South Africa. *Int J*

- Tuberc Lung Dis. 2018; 22: 264–72.
9. Claassens MM, Jacobs E, Cyster E, et al. Tuberculosis cases missed in primary health care facilities: should we redefine case finding? *Int J Tuberc Lung Dis.* 2013; 17: 608–14.
 10. Christian CS, Gerdtham UG, Hompashe D, Smith A, Burger R. Measuring quality gaps in TB screening in South Africa using standardised patient analysis. *Int J Environ Res Public Health.* 2018; 15: 729.
 11. Van der Walt M, Moyo S. The First National TB Prevalence Survey, South Africa 2018: Short report. 2021. Available from: https://www.knowledgehub.org.za/system/files/elibdownloads/2021-02/A4_SA_TPS%20Short%20Report_10June20_Final_highres.pdf. Accessed on 11 October 2021.
 12. Zhou S, Staden Q Van, Toska E. Resource reprioritisation amid competing health risks for TB and COVID-19. *Int J Tuberc Lung Dis.* 2020; 24: 1215–1216.
 13. Gareta D, Baisley K, Mngomezulu T, et al. Cohort Profile Update: Africa Centre Demographic Information System (ACDIS) and population-based HIV survey. *Int J Epidemiol.* 2020; 50: 33–34.
 14. Wong EB, Olivier S, Gunda R, et al. Convergence of infectious and non-communicable disease epidemics in rural South Africa: a cross-sectional, population-based multimorbidity study. *Lancet Glob Health.* 2021; 9: 9–11.
 15. Baisley K, Seeley J, Siedner M, et al. Findings from home-based HIV testing and facilitated linkage after scale up of test and treat in rural South Africa: young people still missing. *HIV Med.* 2019; 20: 704–8.
 16. Tang AM, Chung M, Dong KR, et al. Determining a global mid-upper arm circumference cut-off to assess underweight in adults (men and non-pregnant women). FHI 360/FANTA. Washington, DC; 2020.
 17. Fehr J, Konigorski S, Olivier S, et al. Computer-aided interpretation of chest radiography to

- detect TB in rural South Africa. *npj Digital Medicine*. 2021; 4: 106.
18. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009; 42: 377–81.
 19. Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: Building an international community of software platform partners. *J Biomed Inform*. 2019; 95: 103208.
 20. R Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2018. Available from: <http://www.r-project.org/>
 21. 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.
 22. Nguyen HV, Tiemersma EW, Nguyen HB, et al. The second national tuberculosis prevalence survey in Vietnam. *PLoS ONE*. 2020; 322: 1–15.
 23. 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: 1–19.
 24. 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*. 2020; 72: e1035-e1043.
 25. Turner RD, Chiu C, Churchyard GJ, Esmail H, Lewinsohn DM, Gandhi NR, et al. Tuberculosis Infectiousness and Host Susceptibility. *J Infect Dis*. 2017; 216: S636–43.
 26. Wong EB. It Is Time to Focus on Asymptomatic Tuberculosis. *Clin Infect Dis*. 2020; 72: e1044-e1046.
 27. Narasimhan P, Wood J, Macintyre CR, Mathai D. Risk factors for tuberculosis. *Pulm Med*. 2013; 2013: 828939.
 28. Safari W, Randera-Rees S, Madolo T, et al. Can we find the missing men in clinics? Clinic attendance by sex and HIV status in rural KwaZulu-Natal, South Africa. In: *TB Science, 49th World Conference on Lung Health*. The Hague, The Netherlands; 2018.

29. Hamada Y, Lujan J, Schenkel K, Ford N, Getahun H. Sensitivity and specificity of WHO's recommended four-symptom screening rule for tuberculosis in people living with HIV: a systematic review and meta-analysis. *Lancet HIV*. 2016; 5: e515–23.
30. Kapata N, Chanda-Kapata P, Ngosa W, et al. The Prevalence of Tuberculosis in Zambia: Results from the First National TB Prevalence Survey, 2013–2014. *PLoS ONE*. 2016; 11: e0146392.
31. Migambi P, Gasana M, Uwizeye CB, et al. Prevalence of tuberculosis in Rwanda: Results of the first nationwide survey in 2012 yielded important lessons for TB control. *PLoS ONE*. 2020; 1: 1–12.
32. Kigozi G, Engelbrecht M, Heunis C, Rensburg AJ Van. Household contact non-attendance of clinical evaluation for tuberculosis: a pilot study in a high burden district in South Africa. *BMC Infect Dis*. 2018; 18.
33. McCreesh N, Faghmous I, Looker C, et al. Coverage of clinic-based TB screening in South Africa may be low in key risk groups. *Public Health Action*. 2016; 6: 19–21.
34. Sander MS, Laah SN, Titahong CN, et al. Systematic screening for tuberculosis among hospital outpatients in Cameroon: The role of screening and testing algorithms to improve case detection. *J Clin Tuberc Other Mycobact Dis*. 2019; 15: 100095.
35. Nguyen LH, Codlin AJ, Vo LNQ, et al. An Evaluation of Programmatic Community-Based Chest X-ray Screening for Tuberculosis in Ho Chi Minh City, Vietnam. *Trop Med Infect Dis*. 2020; 5: 185.
36. World Health Organization. WHO consolidated guidelines on tuberculosis. Module 2: screening - systematic screening for tuberculosis disease. Geneva; 2021. Available at: <https://www.who.int/publications/i/item/9789240022676>. Accessed on 6 October 2021.
37. Ramos A, Carvalho T, Guimarães JT. The Importance of Multiple Samples in Mycobacterial Recovery: A 10 - Year Retrospective Study. *Int J Mycobacteriology*. 2019; 8: 175–9.
38. Islam MR, Khatun R, Khaja M, Uddin M, Khan SR. Yield of Two Consecutive Sputum Specimens for the Effective Diagnosis of Pulmonary Tuberculosis. *PLoS ONE*. 2013; 8: 8–11.

TABLES

Table 1: Characteristics of enrolled participants who were sputum culture-positive and/or sputum Xpert Ultra-positive for *Mtb*, clinic and community survey

Characteristic	MGIT positive only		Xpert Ultra positive only
	Clinic (n = 20)	Community (n = 58)	Community (n = 20)
Age, median (IQR)	37 (32–46)	48 (30–64)	53 (43–60)
Male, n (%)	9 (45.0)	28 (48.0)	12 (60.0)
MUAC (cm), median (IQR)	25.6 (23.9–26.0)	27.0 (24.0–30.0)	28.0 (26.0–30.0)
TB treatment history			
On treatment	2 (10.0)	4 (6.9)	4 (20.0)
Previously treated	5 (25.0)	6 (10.3)	11 (55.0)
No history	13 (65.0)	48 (82.2)	5 (25.0)
HIV status, n (%)			
Negative	5 (25.0)*	31 (53.4)	10 (50.0)
Positive	15 (75.0)*	26 (44.8)	10 (50.0)
On ART	15 (100.0)*	21 (80.8)	9 (90.0)
≥1 TB symptom, n (%)	6 (30.0)	13 (22.4)	3 (15.0)
TB resistance profile, n (%)			
Rifampicin monoresistance	1 (5.0)	2 (3.4)	2 (10.0) [†]
Multi-drug resistance	4 (25.0)	9 (15.5)	-
Follow-up TB tests, n (%)			
Positive	12 (60.0)	-	-
Negative	8 (40.0)	-	-

Mtb, *Mycobacterium tuberculosis*; MGIT, Mycobacterial Growth Indicator Tube; Xpert Ultra, Xpert® MTB/RIF Ultra assay; IQR, interquartile range; MUAC, mid-upper arm circumference; TB, tuberculosis; HIV, Human Immunodeficiency Virus
*self-report and clinical record review; †rifampicin resistance detected

Table 2: Characteristics of enrolled participants in clinic (n = 2055) and community (n = 10,320) surveys

	Clinic (n = 2055)	Community (n = 10,320)
Age, median (IQR)	36 (28–48)	38 (23–58)
Female, n (%)	1580 (76.9)	7049 (68.3)
MUAC (cm), median (IQR)	26.0 (25.0–26.0)	27.0 (24.0–30.0)
Previously treated for TB, n (%)	505 (24.6)	1228 (11.9)
On TB treatment at enrolment, n (%)	14 (0.7)	45 (0.4)
HIV status, † n (%)		
Negative	536 (26.1)*	7151 (69.3)
Positive	1479 (72.0)*	3105 (30.1)
On ART	1463 (99.0)*	2714 (87.4)
≥1 TB symptom, n (%)	131 (6.4)	1091 (10.6)
Cough	83 (4.0)	717 (7.0)
Loss of weight	72 (3.5)	281 (2.7)
Night sweats	67 (3.3)	75 (0.7)
Fever	39 (1.9)	18 (0.2)
CAD4TB score >25, n (%)	-	5491 (53.2)
Pregnant, n (%)	Not recorded	328 (3.2)

MUAC, Mid-upper arm circumference; IQR, interquartile range; TB, Tuberculosis; HIV, Human Immunodeficiency Virus; CAD4TB, Computer-aided detection for TB
†40 (1.9%) with missing/unknown HIV status in the clinic survey;
* self-report and clinical record review

Table 3: Univariable analysis of clinic-based survey (N = 2055), showing factors associated with being sputum culture positive (n = 20)			
Characteristic	n sputum culture positive/ N total participants (%)	OR (95% CI)	p-value
Sex			
Female	11/1580 (0.7)		
Male	9/472 (1.9)	2.8 (1.1-6.7)	0.024
Not recorded	0/3		
Age			
< 25 years	2/312 (0.6)		
25 – 44 years	12/1077 (1.1)	1.7 (0.4-7.8)	0.467
> 44 years	6/666 (0.9)	1.4 (0.3-7.0)	0.676
HIV status*			
Negative	4/537 (0.7)		
Positive	15/1473 (1.0)	1.4 (0.5-4.1)	0.577
Unknown	1/45 (2.2)	3.0 (0.3-27.7)	0.326
MUAC			
>= 24cm	15/1822 (0.8)		
< 24cm	5/227 (2.2)	2.7 (1.0-7.5)	0.056
Not measured	0/6		
TB symptoms			
None reported	13/1924 (0.7)		
Reported 1 symptom	1/47 (2.1)	3.0 (0.4-23.0)	0.299
Reported ≥2 symptom	5/131 (3.8)	8.6 (3.0-24.6)	<0.001
OR, odds ratio; CI, confidence interval; HIV, human immunodeficiency virus; TB, Tuberculosis; MUAC, mid-upper arm circumference; * Self-reported HIV status			

Table 4: Univariable and multivariable analysis of community-based survey (N = 10,320), showing factors associated with being sputum culture positive (n = 58)

Characteristic	N sputum culture positive/ n total participants	Univariable analysis				Multivariable analysis			
		OR (95% CI)	p-value	Weighted ¹ OR (95% CI)	p-value	OR (95% CI)	p-value	Weighted ¹ OR (95% CI)	p-value
Sex									
Female	30/7049 (0.4)								
Male	28/3271 (0.9)	2.0 (1.2–3.4)	0.008	1.8 (1.3–2.7)	0.002	2.4 (1.4–4.0)	0.001	2.2 (1.5–3.3)	<0.001
Age									
15–24 years	8/2802 (0.3)								
25–44 years	19/3189 (0.6)	2.1 (1.0–5.1)	0.08	2.8 (1.6–5.2)	<0.001	1.7 (0.7–4.2)	0.2	2.2 (1.2–4.3)	0.011
>44 years	31/4329 (0.7)	2.5 (1.2–5.9)	0.02	3.1 (1.8–5.7)	<0.001	2.7 (1.3–6.3)	0.016	3.3 (1.8–6.1)	<0.001
HIV status									
Negative	31/7151 (0.4)								
Positive on ART	22/2714 (0.8)	1.9 (1.1–3.2)	0.024	1.7(1.1–2.6)	0.01	2.0 (1.1–3.5)	0.022	1.8 (1.2–2.8)	0.008
Positive not on ART	4/391 (1.0)	2.4 (0.7–6.0)	0.11	1.8 (0.7–3.7)	0.20	2.7 (0.8–7.0)	0.077	2.0 (0.8–4.2)	0.080
MUAC									
≥24cm	44/9379 (0.5)								
<24cm	14/941 (1.0)	3.2 (1.7–5.7)	<0.001	3.6 (2.3–5.4)	<0.001				
TB Symptoms									
None reported	45/9229 (0.5)								
Reported 1 symptom	5/717 (0.7)	1.4 (0.5–3.3)	0.4	1.3 (0.6–2.5)	0.5				
Reported >1 symptom	8/374 (2.1)	4.5 (1.9–9.0)	<0.001	6.1(3.6–9.7)	<0.001				

OR, odds ratio; CI, confidence interval; HIV, human immunodeficiency virus; TB, Tuberculosis; MUAC, mid-upper arm circumference; ¹Weights calculated as the inverse probability of participation in the community survey based on age, sex and previous HIV status

FIGURE LEGEND

Figure 1: Summary of enrolment cascade for clinic and community surveys.

Mtb, *Mycobacterium tuberculosis*; CI, confidence interval

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Figure 1

