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Risk-adjusted active tuberculosis case finding strategy in central Ethiopia

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ABSTRACT

Background: The World Health Organization recommends active case finding for tuberculosis (TB). Our study evaluated the targeted screening of household contacts (HHCs) of patients with contagious pulmonary tuberculosis (PTB) in Central Ethiopia.

Methods: The HHCs of patients with microbiologically confirmed PTB were screened for TB symptoms and risk factors for TB transmission. Symptomatic HHCs were subjected to secondary investigation. Antimicrobial resistance was investigated among study participants.

Results: Overall, 112 index patients with TB were included, and 289 HHCs from 89 households were screened. Multidrug-resistant-TB was detected in 2.7% (n=3) of index patients. The routine public health system process did not identify any TB suspects among HHCs. In total, 23.9% (n=69) of HHCs reported ≥1 TB symptom and PTB was confirmed in 2.1% (n=6). Reporting >1 TB symptom (relative risk [RR] 29.4, 95% CI 3.5–245.5, $P<0.001$) and night sweats (RR 27.1, 95% CI 3.2–226.6, $P<0.001$) were associated with the greatest relative risk. Regular alcohol consumption was identified as an individual risk factor for TB among HHCs ($P=0.022$).

Conclusion: The MDR-TB rate among our patients was higher than recently reported for Ethiopia. Enhanced contact tracing using a risk-adjusted approach seems feasible and increases the case detection rate among HHCs of confirmed TB cases.

Introduction

The persistently high global tuberculosis (TB) incidence continues to pose a major threat to achieving the goals of the World Health Organization's (WHO) End TB Strategy (Glaziou et al., 2018; WHO, 2020; Harding, 2020). Although there have been improvements in Ethiopia recently, the country remains one of the high burden countries for TB, with 157,000 cases in 2019 (WHO, 2020). Patients with pulmonary TB (PTB), who account for approximately 50–70% of the country's TB cases (Deribew et al., 2018; Hamusse et al., 2017; Legesse et al., 2021; Mengesha et al., 2021), may transmit the infection to close contacts. Undetected TB cases among these close contacts are common and diagnostic delay leads to ongoing transmission. Therefore, early case detection has been identified as a key strategy to reduce global TB incidence (Reid et al., 2019). In particular, the investigation of household contacts (HHCs) contributes to increased case detection (Ghanaiee et al., 2022; Masiuk et al., 2021; Morrison et al., 2008a).

In Ethiopia, the prevalence of undiagnosed TB in communities is high (2.3 per recognized TB case), and many TB cases are missed or diagnosed late (Arega et al., 2019). However, the (repeated) screening

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of an entire population, as was conducted to collect the data for this study, is not feasible for general implementation. Thus, risk-adjusted active case finding is warranted by screening HHCs of index cases with PTB for signs of active TB, as recommended by WHO and the Ethiopian national TB guidelines (Federal Democratic Republic of Ethiopia Ministry of Health, 2012; WHO, 2012). However, contact tracing requires tremendous effort, and in frequently affected low-income countries, an economical allocation of available resources is necessary. Therefore, the influence of different determinants on the effectiveness of contact tracing, such as identifying high-risk constellations, or precisely defining the target group for contact tracing or the optimal testing strategy, need to be further evaluated to allow optimal use of existing resources.

At the time of data collection, contact tracing in Ethiopia was mostly performed by interviewing TB patients regarding suspicious symptoms among HHCs during an outpatient visit, but without direct investigation. The yield for identifying new TB cases using this approach appears limited and TB experts in the country have suggested an adaptation. Focused screening of high-risk individuals could support earlier case detection at a moderate effort. In this study, we aimed to demonstrate an increase in TB case detection in HHCs of patients newly diagnosed with PTB compared with the standard procedure practiced to date, by using a standardized interview and examination.

Methods

Study design and identification of index patients

Our community-based cross-sectional study was conducted for a 10-month period among HHCs of patients with confirmed PTB. Patients newly diagnosed with smear-positive PTB (PTB+) or smear-negative PTB (PTB-) at the Asella Referral and Teaching Hospital or one of six participating surrounding health centers in the Arsi Zone, Central Ethiopia, served as index cases. The diagnosis was established according to the Ethiopian national guidelines, using light-emitting diode fluorescence microscopy (LED-FM) of sputum samples and/or clinical characteristics.

For study purposes, the diagnosis of PTB in index cases was confirmed by sputum Xpert® MTB/RIF (Cepheid Inc., Sunnyvale, CA, USA) assay for the detection of Mycobacterium tuberculosis (MTB) and resistance to rifampicin and/or TB culture (Fig. 1). Cultures were also examined if Xpert® MTB/RIF assay revealed rifampicin resistance. Patients with LED-FM, Xpert® or culture-confirmed PTB diagnosis were included as index cases. The investigation of the index patients' HHCs was performed independently of the culture result to avoid delays. If confirmation of PTB was not possible, the corresponding data set was excluded. All results generated as part of study investigations were reported to treating physicians.

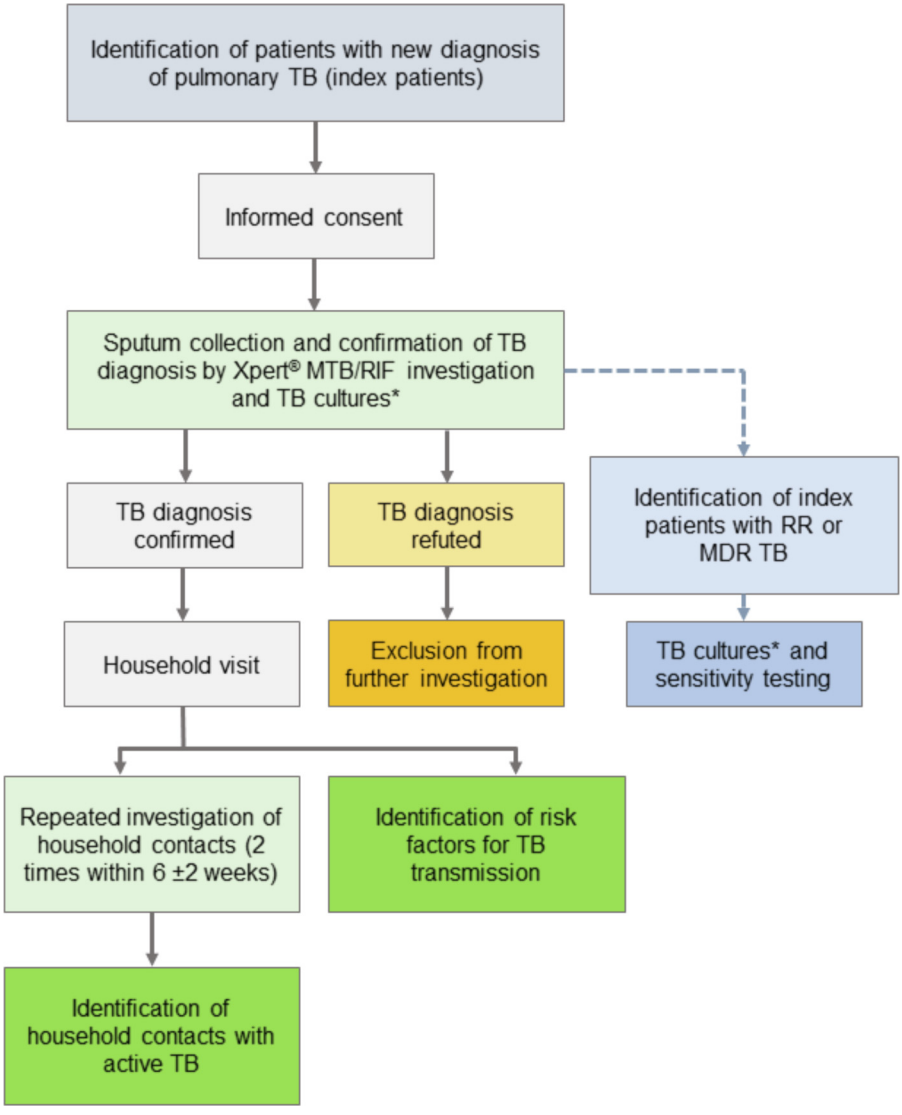

Figure 1. Flow chart of the study protocol; TB = tuberculosis, RR = rifampicin resistance, MDR = multidrug resistance; *TB cultures were investigated for confirmation of Xpert® MTB/RIF-negative smear-positive or smear-negative pulmonary TB or if rifampicin resistance was detected by Xpert® MTB/RIF assay

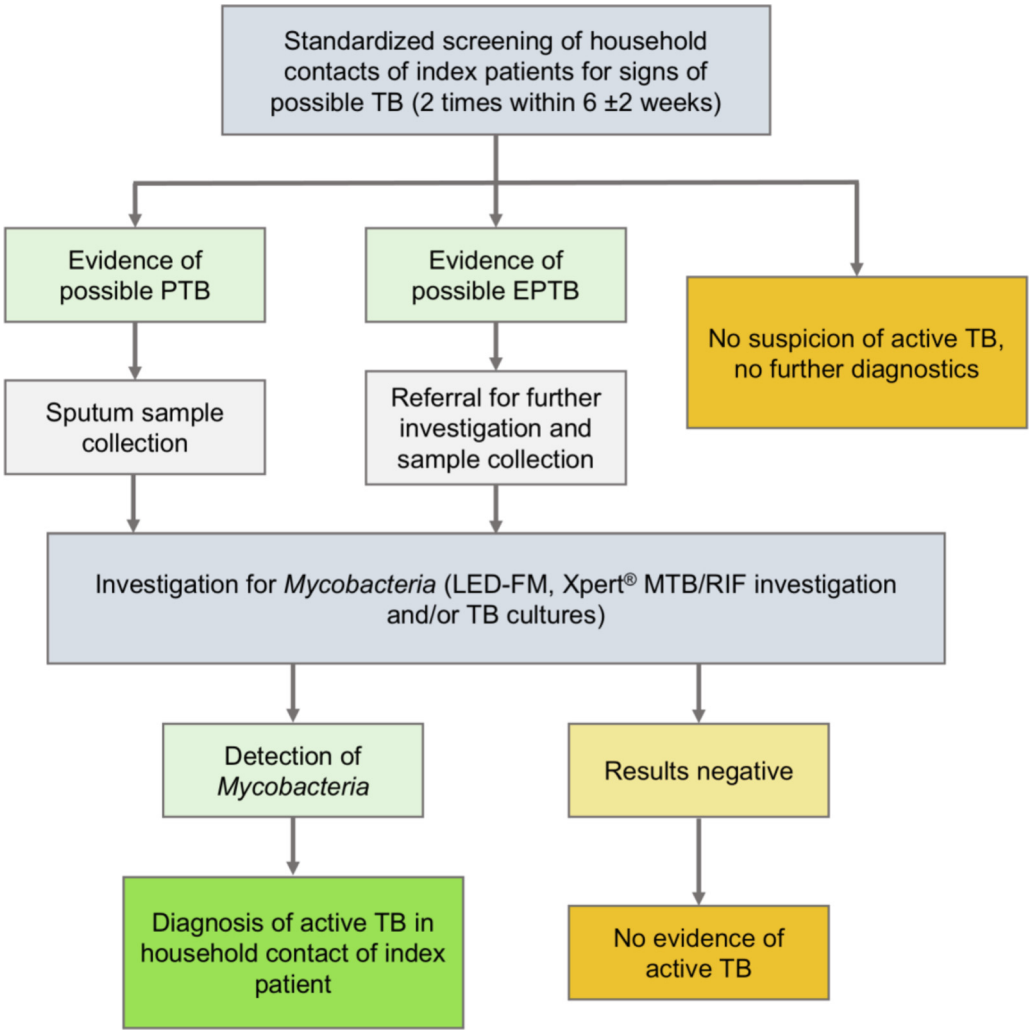

Figure 2. Diagnostic procedure for screening and investigation of symptomatic household contacts (TB = tuberculosis, PTB = pulmonary tuberculosis, EPTB = extrapulmonary tuberculosis, LED-FM = light-emitting diode fluorescence microscopy)

Household visits

The index patients' places of residence were visited (two visits at an interval of 6 ±2 weeks) for identification of risk factors for TB transmission and HHC screening (definition following WHO recommendations WHO, 2012), following a standardized protocol. At each household (HH) visit, all available HHCs were screened for signs of active TB following an established adapted protocol for TB contact tracing (Stapledon et al., 2010).

TB screening

If a study interview or investigation of the HHCs revealed signs of possible TB (ie, history of weight loss, night sweats, low-grade fever, coughing >2 weeks duration, hemoptysis, loss of appetite or swollen lymph nodes), further investigations were performed. In PTB suspects, a spot sputum sample was collected for Xpert® investigation, following WHO recommendations (WHO, 2013). In extrapulmonary TB suspects, referral to the Asella Referral and Teaching Hospital for further investigation was offered, following Ethiopian national guidelines for management of TB (Federal Democratic Republic of Ethiopia Ministry of Health, 2012) (Fig. 2). In special cases, or in the event of discrepant findings, examination of TB cultures from different specimens was optionally available by order of the investigating clinicians. Investigations were repeated if a symptomatic HHC without confirmation of TB in the initial investigations remained symptomatic at the second HH visit. HHCs with a newly established TB diagnosis were referred to the appropriate health facility for treatment.

TB cultures and antimicrobial sensitivity testing

Mycobacterial cultures were processed at the Adama Public Health Research and Referral Laboratory Center in Adama, Ethiopia. The laboratory procedures followed a standardized protocol using Löwenstein-Jensen medium and commercial liquid media preparations (BBL® MGIT® tubes, Becton Dickinson, Franklin Lakes, NJ, USA) and the automated BACTEC® MGIT® 960 mycobacterial detection system (Becton Dickinson) with subsequent line probe assay for antimicrobial sensitivity testing. Susceptibility to isoniazid and rifampicin was assessed using the line probe assay; if resistance to both agents was present, a multidrug-resistant strain of TB was identified by definition (WHO, 2016).

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics, Version 25.0 (IBM Corp. Armonk, NY, USA). The Shapiro-Wilk test was used to assess data distribution and the Mann-Whitney-U-test to compare the median of non-normally distributed independent variables. Chi-square test was used for comparison of categorical variables and the relative

Table 1
Demographic and clinical information of index cases (*n*=112).

Variable	% (n)	Median (IQR)
Gender		
Female	39.3 (44)	
Male	60.7 (68)	
Age in years		28 (22–35)
TB diagnosis		
Pulmonary smear positive	80.4 (90)	
Pulmonary smear negative	19.6 (22)	
Previous history of TB	8.0 (9)	
Rifampicin-resistance in Xpert® MTB/RIF assay	3.6 (4)	
No pretreatment	2.9 (3/103)	
After pretreatment	11.1 (1/9)	
MDR-TB according to AST		
No pretreatment	2.9 (3/103)	
After pretreatment	(0)	
Index patients' TB symptoms		
Weight loss	89.3 (100)	
Night sweats	85.7 (96)	
Cough >2 weeks duration	73.2 (82)	
Loss of appetite	59.8 (67)	
Hemoptysis	19.6 (22)	
Swelling of lymph nodes	5.4 (6)	
No TB symptoms	0	
Co-morbidities / TB risk factors		
None	72.3 (81)	
Regular alcohol consumption	16.1 (18)	
Habit of smoking or regular khat consumption	13.4 (15)	
Known HIV co-infection	8.9 (10)	
Malnutrition (clinical assessment)	2.7 (3)	
Chronic renal disease	0.9 (1)	
Number of HHCs per index patient		4 (2–5)

IQR = interquartile range; HHCs = household contacts; TB = tuberculosis; MDR = multidrug-resistant; AST = antimicrobial sensitivity testing; HIV = Human Immunodeficiency Virus

risk was calculated. Differences were considered statistically significant at $P<0.05$.

Results

Index patients

In total, 144 newly diagnosed PTB patients were evaluated as index patients. Four patients were later excluded because of missing data. Of the remaining 140, 64.3% (*n*=90) were classified as PTB+ and 35.7% (*n*=50) as PTB-. In 56.0% (*n*=28) of PTB- patients the diagnosis could not be confirmed by further examination; therefore, these patients and their HHCs were excluded. For the remaining 112 index patients, the median age was 28 years (interquartile range [IQR] 22–35) and 39.3% were female. Only a small minority (8.0%, *n*=9) had been treated for TB before.

Rifampicin resistance was detected by Xpert® assay in 3.6% (*n*=4) of the index patients. Culturing and antimicrobial sensitivity testing revealed multidrug-resistant (MDR)-TB in 3 of these cases (2.7%). Only one of those patients had been previously treated for TB. In that case, the Xpert® result of rifampicin resistance could not be confirmed (ie, culture-positive but sensitive to rifampicin and isoniazid) (Table 1).

Household contacts

The 112 included index patients reported 431 HHCs (median 4 [IQR 2–5]). However, 142 (32.9%) HHCs from 13 (11.6%) of the HHs could not be investigated because:

- Remote location of HH (54 HHCs from 10 HHs)
- HH investigation denied by index patient (8 HHCs from 3 HHs)
- The HHC was never encountered during the HH visits (*n*=80)

In addition, 10 index patients were living alone; therefore, no HH investigation was conducted. Among the remaining 289 (67.1%) HHCs of 89 index patients screened at least once (Fig. 3), 157 (54.3%) were female and the median age was 18 years (IQR 10–30). Of these HHCs, 168 (58.1%) were investigated at both visits (Table 2), and ≥1 symptom suggestive of TB was present in 23.9% (69 of 289). Of those symptomatic HHCs, 79.7% (55 of 69) were symptomatic at the first HH investigation; however, in 20.3% (14 of 69, 31.1%, or 14 of 45 symptomatic HHCs investigated twice) only the repeated HH investigation revealed TB symptoms. Thus, 8.3% (14 of 168) of HHCs screened twice developed TB symptoms between the two HH visits and would have been missed if only a single HH investigation had occurred.

The most commonly reported symptoms were night sweats (63.8%, 45 of 69) and cough of >2 weeks duration (60.9%, 42 of 69). In 60.9% (42 of 69) of HHCs >1 symptom was present, and symptoms of possible PTB (ie, cough >2 weeks duration or hemoptysis) were present in 62.3% (43 of 69) of the symptomatic HHCs (Table 2).

TB screening among symptomatic household contacts

In total, 45 sputum samples were investigated from 40 symptomatic HHCs (36 during the first and 9 during the second HH investigation). Six HHCs (2 infants <1 year, 1 child, 3 adults) with symptoms of PTB were unable to provide a spot sputum sample and were therefore offered a referral. TB was confirmed by Xpert® assay from sputum samples in 8.9% (4 of 45) of the sputum examinations. Two cases of PTB in infants <1 year old were confirmed, one by Xpert® assay from gastric fluid and the other by the diagnosis of an experienced pediatrician after chest X-ray revealed typical changes. Additionally, 23 symptomatic HHCs without signs of PTB were offered a referral for TB diagnostics. However, only a small minority followed the invitation, and no additional cases of TB were identified. No further information on the subsequent course was available.

Overall, TB diagnosis (all PTB cases) was established in 2.1% (6 of 289) of the screened HHCs from 4.5% (5 of 112) of the investigated HHs (8.7% [6 of 69] of symptomatic HHCs; 14.0% [6 of 43] of HHCs with PTB symptoms, Fig. 3). Notably, only the second HH visit led to TB diagnosis in 2 cases (33.3%, 2 of 6). According to the interview-based standard contact tracing conducted within the Ethiopian healthcare system (see above), none of the HHCs were suspected of having active TB. No cases of resistant TB (rifampicin-resistant- or MDR-TB) were detected among the HHCs.

Risk factors for TB transmission

No significant risk factors for TB transmission were identified when comparing living conditions in HHs with TB transmission to those without (Table 3). Neither were the age of index patients (P=0.879) nor gender (P=0.846) associated with TB transmission within the HH.

All 6 TB cases among HHCs occurred in HHs of an index patient with PTB+, but the threshold for significance was not met (HHs with TB transmission from index patients with PTB+ versus PTB-: 7.0% [5 of 71] versus 0% [0 of 18], P=0.246). There was no difference in the frequency of TB symptoms among HHCs from HHs of PTB+ compared with PTB- index patients (22.7% [52 of 229] versus 28.3% [17 of 60], P=0.227).

Individual risk factors for TB

The greatest relative risk (RR) for TB was associated with the presence of >1 symptom (RR 29.4; 95% CI 3.5–245.5; $P<0.001$) and with the presence of night sweats (RR 27.1; 95% CI 3.2–226.6; $P<0.001$). Also, regular alcohol consumption (according to self-reporting) was associated with TB (RR 8.1; 95% CI 1.1–60.2; P=0.022). No other risk factors were identified (Table 2).

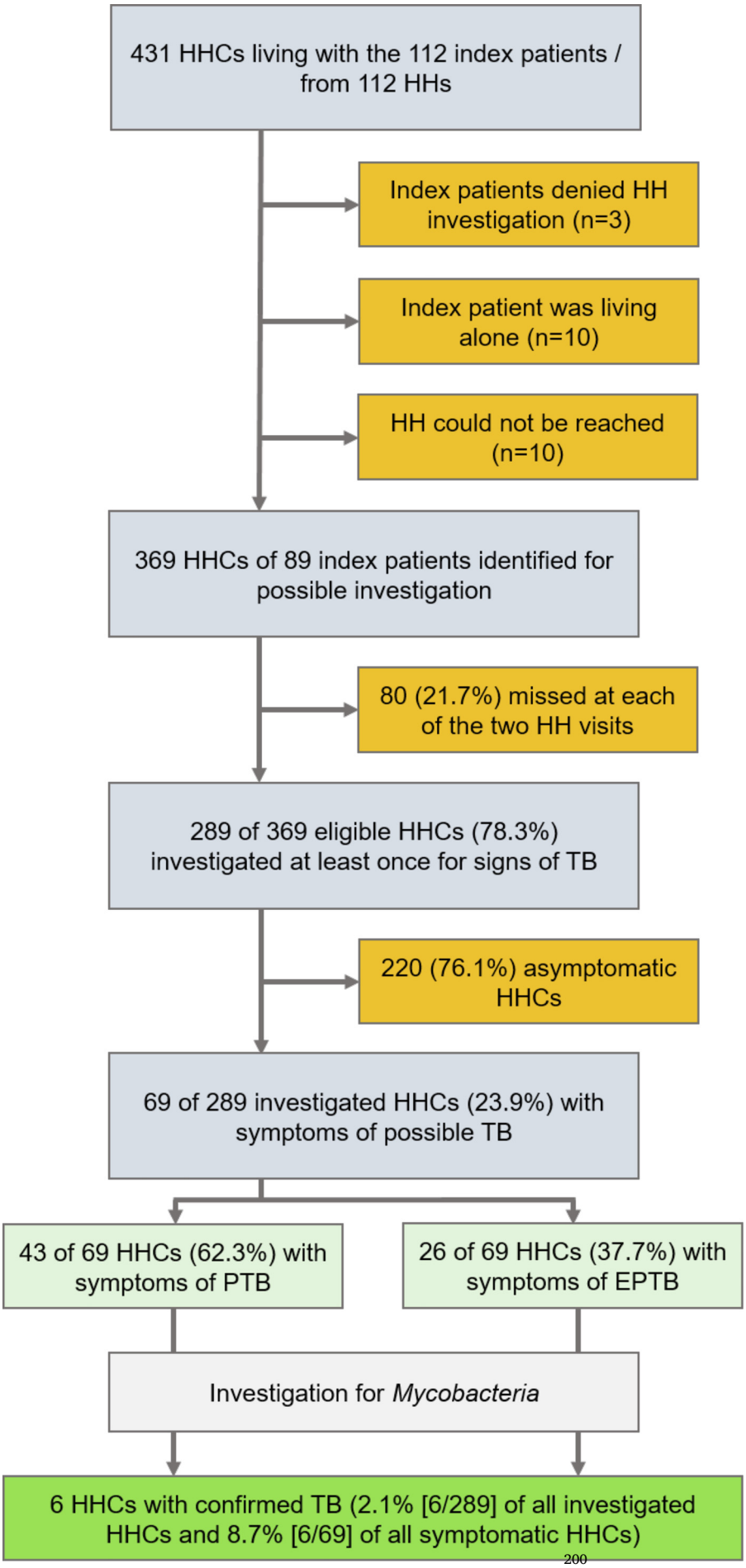

Figure 3. Outcome of household investigation (HHC = household contact, HH = household, TB = tuberculosis, PTB = pulmonary tuberculosis, EPTB = extrapulmonary tuberculosis)

Table 2
General, demographic and clinical information of household contacts.

Variable	All HCCs (*n*=289)	Comparison according to TB diagnosis			
		Confirmed TB (*n*=6)	Without TB (*n*=283)	*p*-value	RR (95% CI)
Gender in % (n)				0.153	
Female	54.3 (157)	83.3 (5)	53.7 (152)		
Male	45.7 (132)	(1)	46.3 (131)		
Median age (IQR) in years	18 (10–30)	25.5 (6.6–29)	18 (10–30)	0.855	
Age groups (years) in % (n)				0.622	
<18	48.1 (139)	33.3 (2)	48.4 (137)		
18-65	48.1 (139)	66.7 (4)	47.7 (135)		
>65	3.8 (11)	(0)	3.9 (11)		
Previous TB treatment in % (n)	0.138				
Yes	2.4 (7)	(1)	2.1 (6)		
No	97.6 (282)	83.8 (5)	97.9 (277)		
HHC investigation at HH visits	0.906				
Both visits	58.1 (168)	50.0 (3)	58.3 (165)		
1st visit only	41.5 (120)	50.0 (3)	41.3 (117)		
2nd visit only	(1)	(0)	(1)		
Symptoms of possible TB in % (n)					
>1 symptom present	14.5 (42)	83.3 (5)	13.1 (37)	**<0.001***	29.4 (3.5; 245.5)
Night sweats	15.6 (45)	83.3 (5)	14.1 (40)	**<0.001***	27.1 (3.2; 226.6)
Cough >2 weeks duration	14.5 (42)	50.0 (3)	13.8 (39)	**0.042***	5.9 (1.2; 28.2)
Low grade fever	13.5 (39)	66.7 (4)	12.4 (35)	**0.004***	12.8 (2.4; 67.7)
Hemoptysis	5.2 (15)	33.2 (2)	4.6 13)	**0.033***	9.1 (1.8; 46.0)
Loss of appetite	4.8 (14)	33.2 (2)	4.2 (12)	**0.029***	9.8 (2.0; 49.1)
Weight loss	3.1 (9)	33.3 (2)	2.5 (7)	**0.012***	15.6 (3.3; 74.2)
Swelling of lymph nodes	(1)	(0)	(1)	0.979	
Risk factors for TB / chronic diseases in % (n)					
No known risk factors	95.2 (275)	83.3 (5)	92.6 (262)	0.398	
Chronic disease present	4.8 (14)	(0)	4.9 (14)	0.576	
Regular alcohol consumption	2.4 (7)	16.7 (1)	2.1 (6)	**0.022***	8.1 (1.1; 60.2)
Regular tobacco smoking	1.0 (3)	(0)	1.1 (3)	0.800	

HHCs = household contacts; TB = tuberculosis; RR = relative risk, CI = confidence interval IQR = interquartile range; HH = household;

Discussion

The WHO recommends contact tracing among close contacts of contagious TB patients (WHO, 2012). Its potential to help reduce TB transmission in Ethiopia is great; a previous investigation found that 2.5 undetected TB cases could be identified through active case finding per one passively detected case (Yimer et al., 2009). However, the most effective and economical testing strategy is unclear. Therefore, we evaluated a targeted case-finding approach in HHCs of presumptively contagious PTB patients, in contrast to the commonly practiced approach in the country to query TB patients about signs of TB among their HHCs. This approach was chosen to achieve an optimal yield with moderate human and financial resources through targeted screening of individuals at risk. However, mobile staff trained in recognizing TB symptoms and sputum sample collection is required. The relatively widespread availability of the Xpert® MTB/RIF assay and the associated ease of sample logistics simplifies the study approach, as no live *Mycobacteria* need to be examined.

Following the targeted screening approach, active TB was identified in 2.1% of the HHCs of TB index patients. This rate differed from the 4.5% TB rate (microbiologically confirmed TB 2.3%) described in a systematic review of TB screening in low and middle-income countries (Morrison et al., 2008b). Different living conditions and routines, such as Ethiopians' habit of spending much of the day outside enclosed spaces, may play a role in explaining the variations. In addition, to optimize resources and following WHO recommendations (WHO, 2013), only one spot sputum examination was performed in PTB suspects, potentially limiting the sensitivity. Many HHCs with extrapulmonary symptoms did not present for further evaluation in the hospital and were lost to follow-up.

Notably, all TB cases were diagnosed in HHCs from HHs of index patients with PTB+ and pulmonary symptoms. The case-finding rate in HHCs with pulmonary symptoms was substantial (14%). Thus, HHCs of smear-positive index patients with pulmonary symptoms were at the highest risk for TB and could therefore be the subject of targeted screening. In contrast, no TB cases were detected among HHCs from index patients with PTB- (culture or Xpert® MTB/RIF-confirmed). The repetition of TB screening yielded a relevant increase in case detection. A second HH investigation seems reasonable to increase the rate of encountered and investigated HHCs; one-third of the newly identified TB cases were detected only at the repeated HH investigation.

Our study identified no risk factors for TB transmission on the HH level. Reporting >1 TB symptom and night sweats as a single symptom were associated with the highest individual RR. Also, regular alcohol consumption was associated with an increased risk for TB. No data on nutritional status or HIV status were available.

Remarkably, not a single TB suspect was identified through the contact tracing procedure commonly followed in Ethiopia, in which only index patients are asked about TB symptoms among their HHCs. Therefore, adjusting the approach seems advisable, considering that 23.4% of the HHCs screened in our study did report TB symptoms. In addition, the clinical diagnosis of smear-negative PTB in index patients through the general healthcare system was confirmed by further testing (eg, PCR) in only 44% of cases. This finding should encourage us to question the diagnosis of PTB in the case of negative LED-FM and to consider further differential diagnoses, especially where no improvement is seen with TB treatment.

Our investigation revealed MDR-TB in 3 patients with PTB without prior TB treatment. This MDR-TB rate of 2.7% in previously untreated patients is significantly higher than the 0.7% recently reported in Ethiopia (WHO, 2020) but reflects the local TB drug resistance rate reported by Hamusse et al. (Hamusse et al., 2016). This finding should prompt intensified surveillance and possibly primary screening for MDR-TB and close monitoring of patients for response to standard TB treatment.

Table 3
Household information and living conditions in households of index patients with confirmed pulmonary TB (*n*=89).

Variable	Overall	Comparison of HHs according to TB confirmation among HHCs		
		≥1 TB case among HHCs (*n*=5)	No TB among HHCs (*n*=84)	*p*-value
Housing type in % (n)				0.670
Hut	11.2 (10)	100 (5)	12.7 (10)	
House	82.0 (73)	(0)	86.1 (68)	
Unknown / missing data	5.6 (5)	(0)	7.1 (6)	
Median number (IQR) of people living in the HH		0.278		
	5 (4–6)	4 (4-5)	5 (4–6)	
Area of HH in % (n)				0.194
Urban	61.8 (55)	100 (5)	59.5 (50)	
Rural	37.1 (33)	(0)	39.3 (33)	
Unknown / missing data	(1)	(0)	(1)	
Number of bedrooms in % (n)			0.363	
1 bedroom	73.0 (65)	60.0 (3)	73.8 (62)	
>1 bedroom	18.0 (16)	40.0 (2)	16.7 (14)	
Unknown / missing data	9.0 (8)	(0)	9.5 (8)	
Source of drinking water in % (n)			0.914	
Tab water	91.0 (81)	100 (5)	90.5 (76)	
Spring water	4.5 (4)	(0)	4.8 (4)	
River / Lake	2.2 (2)	(0)	2.4 (2)	
Unknown / missing data	2.2 (2)	(0)	2.4 (2)	
Shared HH with livestock in % (n)			0.826	
Yes	5.6 (5)	(0)	6.0 (5)	
No	93.3 (83)	100 (5)	92.9 (78)	
Unknown / missing data	(1)	(0)	(1)	
Housing with window in % (n)			0.487	
Yes	78.7 (70)	100 (5)	77.4 (65)	
No	16.9 (15)	(0)	17.9 (15)	
Unknown / missing data	4.5 (4)	(0)	4.8 (4)	
Kitchen within living room in % (n)			0.826	
Yes	5.6 (5)	(0)	6.0 (5)	
No	93.3 (83)	100 (5)	92.9 (78)	
Unknown / missing data	(1)	(0)	(1)	
Sanitation in % (n)				0.487
Water toilet	11.2 (10)	(0)	11.9 (10)	
Pit latrine	78.7 (70)	100 (5)	77.4 (65)	
No access to toilet	10.1 (9)	(0)	10.7 (9)	

HH = household; HHC = household contact.

Conclusion

Our study suggests that improvement in contact tracing in Ethiopia is warranted since the current practice failed to reliably identify TB suspects among studied HHCs. The HHCs of patients with smear-positive PTB and pulmonary symptoms are at greatest risk for TB and should have the highest priority for targeted screening measures. In addition, unrecognized MDR mycobacterial strains may circulate more frequently in Ethiopia than previously estimated. Therefore, intensified surveillance of MDR-TB in the study region seems appropriate.

Declaration of Competing Interest

All authors declare that they have no conflicts of interest.

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Ethical approval statement

This study was conducted in accordance with the Declaration of Helsinki. Ethical clearance was obtained from the Ethical Review Board of Arsi University, Ethiopia (protocol number A/CHS/RC/10/15). All participants or legal guardians (if appropriate) gave informed consent for study participation, which neither delayed nor affected TB treatment.

Author contributions

Andre Fuchs: Study design, data acquisition, analysis and interpretation of data, manuscript preparation and revision

Tafese Beyene Tufa: Study design, data acquisition, analysis and interpretation of data, manuscript revision and approval

Frieder Pfäfflin: Study design, manuscript revision and approval

Andreas Schönfeld: Data acquisition, manuscript revision and approval

Tamara Nordmann: Data acquisition, manuscript revision and approval

Fikru Melaku: Data acquisition and analysis, manuscript approval

Abebe Sorsa: Data acquisition, manuscript approval

Hans Martin Orth: Data analysis, manuscript revision and approval

Tom Luedde: Manuscript revision and approval

Dieter Häussinger: Manuscript revision and approval

Torsten Feldt: Study design, analysis and interpretation of data, manuscript revision and approval

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