

Etiologic Investigation of Patients Diagnosed with Bacteriologically Unconfirmed Tuberculosis in Tanzania

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Abstract. Globally, half of patients with pulmonary tuberculosis (PTB) are diagnosed clinically without bacteriologic confirmation. In clinically diagnosed PTB patients, we assessed both the proportion in whom PTB could be bacteriologically confirmed by reference standard diagnostic tests and the prevalence of diseases that mimic PTB. We recruited adult patients beginning treatment of bacteriologically unconfirmed PTB in Moshi, Tanzania, in 2019. We performed mycobacterial smear, Xpert MTB/RIF Ultra, and mycobacterial culture, fungal culture, and bacterial culture on two induced sputum samples: fungal serology and computed tomography chest scans. We followed participants for 2 months after enrollment. We enrolled 36 (63%) of 57 patients with bacteriologically unconfirmed PTB. The median (interquartile range) age was 55 (44–67) years. Six (17%) were HIV infected. We bacteriologically confirmed PTB in 2 (6%). We identified pneumonia in 11 of 23 (48%), bronchiectasis in 8 of 23 (35%), interstitial lung disease in 5 of 23 (22%), pleural collections in 5 of 23 (22%), lung malignancy in 1 of 23 (4%), and chronic pulmonary aspergillosis in 1 of 35 (3%). After 2 months, 4 (11%) were dead, 21 (58%) had persistent symptoms, 6 (17%) had recovered, and 5 (14%) were uncontactable. PTB could be bacteriologically confirmed in few patients with clinically diagnosed PTB and clinical outcomes were poor, suggesting that many did not have the disease. We identified a high prevalence of diseases other than tuberculosis that might be responsible for symptoms.

INTRODUCTION

Tuberculosis (TB) is one of the leading causes of global morbidity and mortality, with > 1.4 million deaths during 2019.¹ The World Health Organization (WHO) case definitions of TB include bacteriologically confirmed cases, where a biologic specimen is positive by smear microscopy, culture, or approved rapid diagnostic tests. Alternatively, TB cases can be clinically diagnosed where the patient has not been bacteriologically confirmed but has been diagnosed with active TB by a clinician who has decided to give TB treatment.² In 2019, approximately 6 million, or 84% of global TB cases, were pulmonary TB (PTB), with the remainder extrapulmonary TB. Of those with PTB, 57% were bacteriologically confirmed, with the remainder clinically diagnosed.¹ The proportion of PTB that is bacteriologically unconfirmed varies substantially by country, but in many well-resourced settings less than 10% of PTB is unconfirmed.³ Documented outcomes of patients with TB are frequently worse among those with clinically diagnosed TB compared with those with bacteriologically confirmed TB, with recent data indicating up to 10% mortality at 6 months among those diagnosed clinically compared with < 5% among bacteriologically confirmed cases.⁴ Data suggest this increased mortality cannot be fully explained by comorbidities,^{4,5} raising the possibility that unrecognized diseases mimicking TB are contributing to individual poor outcomes and compromising programmatic goals.

Nearly half of all PTB cases are clinically diagnosed because of limitations among diagnostic tests as well as the

lack of availability.⁶ Notably, these tests rely on the collection of sputum, which is not feasible in all patients. Furthermore, each test has its limitations. Mycobacterial culture of multiple sputum samples, the reference standard diagnostic test for PTB,⁷ is resource intense and technically challenging, and consequently widely unavailable in many low-resource, high-TB incidence countries. Sputum smear microscopy, historically the most commonly used diagnostic test for PTB, has low sensitivity among patients with paucibacillary disease, such as children and those with HIV infection.⁸ Molecular detection by Xpert MTB/RIF or Xpert MTB/RIF Ultra have higher sensitivity compared with sputum microscopy, but the sensitivity remains lower than that of culture.⁹ Taken together, clinicians in high-TB incidence settings are often faced with making PTB treatment decisions in the context of a limited or negative diagnostic workup. To avoid undertreatment of PTB, clinical diagnosis and treatment of chronic respiratory diseases as PTB is common.¹ This approach is understandable given the infection risk to others and potential morbidity of untreated PTB along with the recognition that the best available diagnostic tools may not diagnose all patients with PTB when treatment decisions are needed.¹⁰

Therefore, the symptoms of some patients with clinically diagnosed PTB may in fact be due to diseases other than TB,¹¹ but knowledge of the epidemiology of diseases that mimic PTB in low-resource, high-TB incidence settings is limited. Failure to diagnose and treat these conditions may explain the poorer treatment outcomes for these patients. Available reports suggest that other diseases with similar manifestations, such as aspergillosis,¹² bronchiectasis,¹³ histoplasmosis,¹⁴ and *Pneumocystis jiroveci* pneumonia are underrecognized.¹⁵ Standard diagnostic tests for these conditions are typically unavailable in many high-TB incidence countries; and current diagnostic and treatment guidelines,

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such as those provided by the WHO, do not promote consideration or testing for these conditions among patients suspected of having PTB. For these reasons, an understanding of the epidemiology of diseases that mimic PTB is an important step toward redesigning present diagnostic and treatment pathways, and such efforts may improve clinical outcomes for patients across many low-resource settings.

Tanzania is a lower middle-income country in East Africa, and in 2019 had an estimated incidence of TB of 237 (uncertainty interval 112–408) cases per 100,000 population.¹ TB culture is not widely available, so sputum smear microscopy and more recently Xpert MTB/RIF are used to bacteriologically confirm TB. Approximately half of all PTB diagnoses are not bacteriologically confirmed, and this proportion has not fallen since the widespread introduction of Xpert MTB/RIF testing of sputum.^{1,16} In this context, we sought to investigate patients beginning treatment of PTB without bacteriologic confirmation, to assess whether PTB could be confirmed via induced sputum specimens and to systematically assess the presence of diseases that might mimic PTB.

MATERIALS AND METHODS

We conducted a prospective cohort study at two referral hospitals, Mawenzi Regional Referral Hospital and Kilimanjaro Christian Medical Center (KCMC) in Moshi, Tanzania from July 9 through October 21, 2019. Moshi (population > 180,000) is the administrative center of the Kilimanjaro region (population > 1.6 million). Mawenzi Regional Referral Hospital is a 300-bed regional hospital that serves the Kilimanjaro region and KCMC is a 630-bed zonal referral hospital that serves the northern zone of Tanzania (population > 15 million). Xpert MTB/RIF of sputum samples was the

standard diagnostic test for PTB at our study sites during the study period.

Enrollment criteria. We prospectively screened all patients beginning TB treatment at each site. Patients were eligible for enrollment if they were beginning treatment of PTB as a clinically diagnosed case without bacteriologic confirmation²; that is, they did not have a biological specimen that was positive by smear microscopy, culture, or a WHO-approved rapid diagnostic test (such as Xpert MTB/RIF). We included any patient diagnosed according to the treating physician's judgment, and included patients whose sputum samples had tested negative and those who were unable to provide sputum samples. Patients with impaired consciousness, requiring > 3 L/minute supplemental oxygen, with evidence of shock, or with uncontrolled asthma were excluded because of concerns they would be unable to safely complete sputum induction. Participants were enrolled within 24 hours of beginning treatment.

Study procedures. After providing informed written consent, participants were administered a standardized questionnaire of symptoms, treatments taken, past medical history, and social risk factors for respiratory disease. Standardized physical examination was performed by a trained clinical officer. Participants underwent a cascade of investigations as shown in Figure 1. First, sputum induction was performed using 7% hypertonic saline via the DeVilbiss UltraNeb 2000 (DeVilbiss, Port Washington, NY) ultrasonic nebulizer. We considered an adequate sputum volume to be ≥ 5 mL.¹⁷ Two samples were collected at least 2 hours apart, pooled, and tested as one.¹⁸ Participants with negative initial mycobacterial tests (sputum microscopy and molecular tests as described below) were requested to provide blood for fungal serology and undergo a computed tomography (CT) chest scan, and induced sputum was processed for bacterial and fungal pathogens. All participants were offered counseling

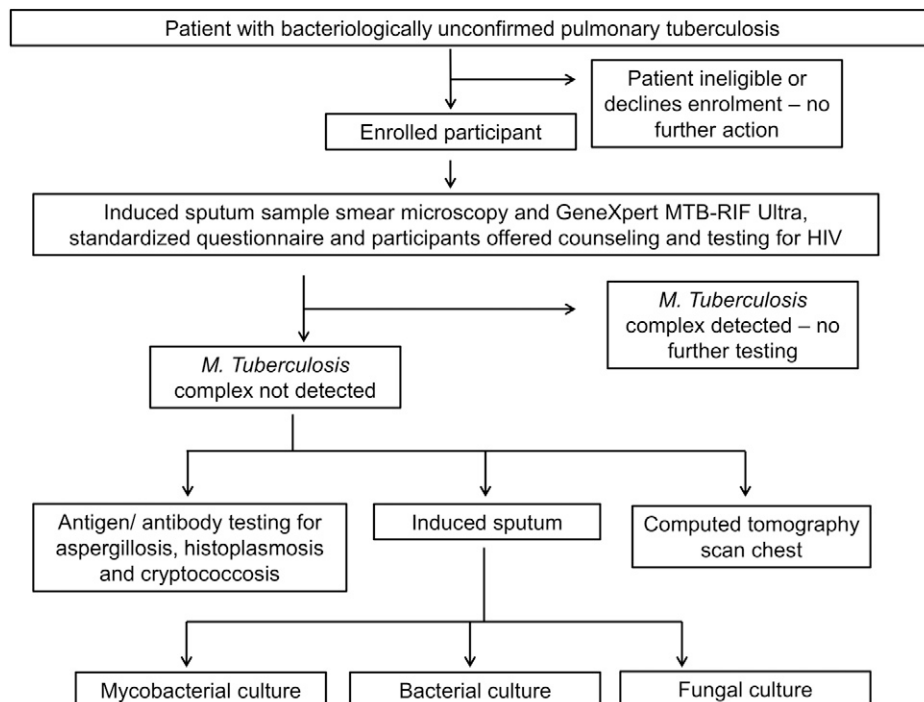


FIGURE 1. Investigation protocol for participants with bacteriologically unconfirmed pulmonary tuberculosis, northern Tanzania, 2019.

and testing for HIV by the treating clinicians immediately prior to enrollment, with our study recording participant-reported HIV infection status.

Laboratory testing. Sputum testing and cryptococcal antigen testing were performed at the Kilimanjaro Clinical Research Institute, Moshi, Tanzania. *Aspergillus* and *Histoplasma* serological testing was performed by New South Wales Pathology, Sydney, Australia.

Sputum mycobacterial testing. Approximately two-thirds of the sputum sample was apportioned for mycobacterial testing. Sputum was tested for *Mycobacterium tuberculosis* complex using microscopy with TB Fluorescent Stain (Becton Dickinson, Franklin Lakes, NJ) using the standard technique; the Xpert MTB/RIF Ultra assay (Cepheid, Sunnyvale, CA) according to manufacturer protocols; and mycobacterial culture using the BACTEC Mycobacteria Growth Indicator Tube (MGIT) system on the MGIT BACTEC 960 (Becton Dickinson) with a maximum incubation of 42 days. Positive mycobacterial cultures were confirmed as TB using the GenoType MTBDRplus (Hain Life Sciences, Nehren, Germany).

Sputum bacterial culture. Approximately one-third of the sputum sample was apportioned for bacterial and fungal testing. Sputum was processed using standard streak plate methods. Gram stain was performed directly on the most purulent portion of sputum samples. A purulent portion of sputum was inoculated onto sheep blood agar, MacConkey

agar, chocolate agar, and colistin nalidixic acid agar and then cultured at 35–37°C in 5% CO₂. Isolate identification was performed using standard biochemical methods.

Sputum fungal culture. Sputum was inoculated onto Sabouraud dextrose agar and cultured at 30 and 36°C.

Fungal serology. Cryptococcal antigen level was measured using the Latex Cryptococcal Antigen Detection System assay (Immuno-Mycologics, Norman, OK). Serum samples were stored at –80°C and tested for *Aspergillus* IgG using the CAP fluoroenzyme immunoassay system and for total *Histoplasma* antibody by immunodiffusion.

CT chest scanning. Participants underwent CT scanning of the chest using the Siemens Somatom Definition AS+ scanner (Siemens AG, Munich, Germany). CT scans were read by two radiologists (A. S. and R. T.). A single radiologist (R. T.) categorized CT results according to a priori case definitions (Table 1). Participants and the treating clinicians received a report of the results of the scan.

Case definitions. We assigned diagnoses using standardized disease definitions as described in Table 1.^{19–26} Participants could accrue > 1 diagnosis.

Follow-up procedures. Participants attended a follow-up visit 2 months after enrollment. A study clinical officer administered a standardized questionnaire covering current symptoms, health status, and additional treatment and performed a standardized physical examination. For patients unable to

TABLE 1
Case definitions for diseases among patients who began treatment of PTB without bacterial confirmation

Disease	Relevant investigations	Definition
Mycobacterial infection		
TB	Mycobacterial culture	Positive Xpert MTB/RIF or culture of <i>Mycobacterium tuberculosis</i> complex
Nontuberculous mycobacterial infection	Mycobacterial culture	Culture of nontuberculous mycobacteria
Bacterial infection		
Bacterial pneumonia	CT chest, sputum culture, blood culture	Consolidation on CT chest, with negative tests for <i>M. tuberculosis</i> complex and fungal lung disease
Bronchiectasis	CT chest	On CT chest: the internal diameter of the bronchus is larger than that of its accompanying vessel, or the bronchus fails to taper in the periphery of the chest
Lung abscess	CT chest, sputum culture	Evidence of abscess formation on CT chest, with or without culture of bacterial pathogen on sputum culture. Negative tests for <i>M. tuberculosis</i> complex and fungal lung disease
<i>Nocardia</i> pneumonia	Sputum gram stain and culture, blood culture	Presence of <i>Nocardia</i> on gram stain or culture
Fungal infection		
CPA	<i>Aspergillus</i> IgG ELISA	Radiological findings in keeping with CPA definitions, plus either culture of <i>Aspergillus</i> species or a positive <i>Aspergillus</i> IgG
Cryptococcosis	Cryptococcal antigen test	Culture of <i>Cryptococcus</i> from sputum or a positive cryptococcal antigen test
Histoplasmosis	<i>Histoplasma</i> IgG serology	Culture of <i>Histoplasma</i> from sputum or a positive <i>Histoplasma</i> serology
Diffuse noninfectious		
HP	CT chest, exposure history	CT chest findings in keeping with HP (with or without relevant exposure history), and negative <i>M. tuberculosis</i> complex and fungal tests
Interstitial lung disease	CT chest	CT chest findings in keeping with interstitial lung disease, and negative <i>M. tuberculosis</i> culture and fungal tests
Pneumoconiosis	CT chest, exposure history	CT chest findings in keeping with pneumoconiosis, occupational mining exposure history, and negative <i>M. tuberculosis</i> complex and fungal tests
Malignancy	CT chest	CT chest findings in keeping with malignancy

CPA = chronic pulmonary aspergillosis; CT = computed tomography; HP = hypersensitivity pneumonitis; PTB = pulmonary tuberculosis.

attend a follow-up in person, a telephone questionnaire was administered. If study staff were unable to contact a participant, their next of kin was contacted to ascertain vital status.

Data handling and statistical analysis. Questionnaire and physical examination data were entered onto the Open Data Kit platform.²⁷ Laboratory testing data were entered using the Cardiff OpenText TeleForm System (Waterloo, Canada). Radiology data were entered into a Microsoft Excel spreadsheet (Microsoft Corp, Seattle, WA). All data were analyzed in Stata version 16 (StataCorp, College Station, TX). Continuous variables were expressed using medians and interquartile ranges (IQR). Categorical variables were expressed as frequencies and percentages.

RESULTS

Baseline sociodemographic and clinical characteristics.

Among 135 screened patients beginning treatment of TB, 125 (93%) had been diagnosed with PTB and 57 (42%) were bacteriologically unconfirmed and therefore eligible for our study (Figure 2). Of those eligible, 36 (63%) consented to participate. The median (IQR) age was 55 (44–67) years, with 21 (58%) male (Table 2). All participants reported a cough for a median (IQR) duration of 30 (21–90) days, with 19 (53%) reporting spontaneous sputum production. Twenty (56%) reported fevers, and 17 (47%) reported weight loss. Thirty-three (92%) reported taking antibacterial medication for their

current illness, with 18 (50%) taking two courses and two (6%) taking at least three courses. The most commonly reported antimicrobial drugs consumed were amoxicillin (10; 28%) and ampicillin-cloxacillin (9; 25%), with two (6%) taking ciprofloxacin, an antibacterial with some expected activity against *M. tuberculosis* complex. Three (8%) participants reported taking antifungal medication, and three (8%) reported taking a previous course of TB medication during the current illness.

Twenty-seven (75%) of participants reported no comorbidities. Reported comorbidities included six (17%) with HIV infection, all of whom were taking antiretroviral medication, and asthma, three (8%). Of those with HIV, two (33%) had a productive cough, and for those without HIV, 17 (57%) had a productive cough. We identified six (17%) participants who had completed at least one course of TB medication for a previous illness, and two (6%) who had completed two courses. Sixteen (44%) were current or ex-smokers, with a median (IQR) exposure of 10 (4–16) pack-years. Twenty-one (58%) participants were subsistence farmers, and eight (22%) were current or ex-miners.

Ten (28%) participants had a body mass index (BMI) < 18.5 kg/m², and nine (25%) had a mid-upper arm circumference < 22 cm. One (3%) participant had a temperature ≥ 38.0°C. Eleven (31%) participants had a peripheral oxygen saturation (SpO₂) < 92% when measured on ambient air.

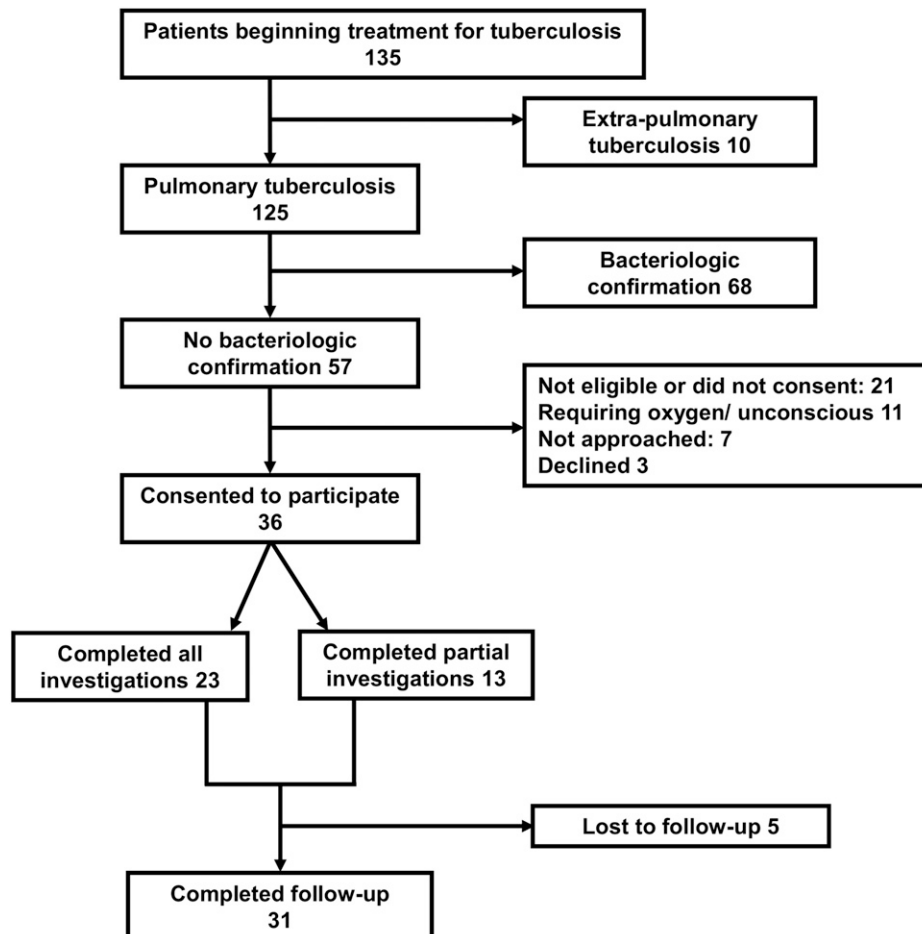


FIGURE 2. Study flow diagram indicating recruitment and follow-up of patients beginning treatment of tuberculosis, northern Tanzania, 2019.

TABLE 2
Characteristics of patients who began treatment of PTB without bacterial confirmation (N = 36)

Characteristic	n (%)
Median (IQR) age (years)	55 (44–67)
Male sex	21 (58)
Occupation	
Subsistence farmer	21 (58)
Business person	7 (19)
Healthcare worker	2 (6)
Other	6 (17)
Current or ex-miner	8 (22)
Cough	36 (100)
Sputum production	19 (53)
Hemoptysis	9 (25)
Median (IQR) duration of cough (days)	30 (21–90)
Dyspnea	26 (72)
Fever	20 (56)
Median (IQR) fever duration (days)	7 (5–21)
Weight loss	17 (47)
Sweats	8 (22)
Median (IQR) body mass index	21.6 (18.2–23.8)
Median (IQR) SpO ₂ (%)	94 (81–98)
Digital clubbing	1 (2.8)
Palpable lymphadenopathy	3 (8.3)
Median (range) mid-upper arm circumference	25.0 (21.5–28.5)

IQR = interquartile range; N = number of study participants with relevant data available; n = number of participants displaying the relevant characteristic, symptom, or sign; PTB = pulmonary tuberculosis; SpO₂ = peripheral oxygen saturation; TB = tuberculosis.

Prevalence of PTB and other diseases. We successfully induced an adequate sputum sample from 35 (97%) participants. The median (range) sputum volume was 9 (5–20) mL. We bacteriologically confirmed TB in two (6%). Of 34 participants eligible to proceed to further investigations, chest CT scans were completed and able to be interpreted in 23 (68%), with seven (20%) not completing chest CT scans; data storage or transfer problems precluded classification of scans in four (12%).

The most commonly identified diseases among the 23 participants who completed the full investigations were pneumonia (11; 48%) and bronchiectasis (8; 35%), all of whom also had evidence of pneumonic consolidation (Table 3). In addition, 10 (44%) had radiologic evidence of previous exposure to TB, including six (75%) of those with bronchiectasis. In the 11 participants diagnosed with pneumonia, we cultured *Pseudomonas aeruginosa* in three (27%), *Klebsiella pneumoniae* in three (27%), and other gram-negative organisms in three (27%). *Pseudomonas aeruginosa* was also cultured in two (25%) of the participants with bronchiectasis and two (40%) with pleural disease. In addition, *P. aeruginosa* was cultured from six people who did not meet criteria for any diagnosis, of whom five (83%) had not had a CT chest scan.

Participant follow-up. We completed follow-up at 2 months for 31 (86%) participants, with 20 (56%) completing in-person follow-up, seven (19%) completing telephone follow-up, and four (11%) confirmed as deceased, none of whom had bacteriologically confirmed TB. Among decedents, we diagnosed lung abscess in one (25%) and lung malignancy and concomitant pneumonia in one (25%). The other two (50%) did not undergo CT chest scans, and no diagnoses were reached. Of living participants who completed follow-up, 21 (78%) had persistent symptoms, and six (22%) reported resolution of symptoms. Both participants in whom we bacteriologically confirmed PTB reported

TABLE 3
Diagnoses of patients who began treatment of PTB without bacterial confirmation

Diagnosis	N	n	%
TB	35	2	6
Nontuberculous mycobacterial infection	35	0	0
Bacterial pneumonia (without bronchiectasis)	23	11	48
Bronchiectasis	23	8	35
Lung abscess	23	1	4
<i>Nocardia</i> pneumonia	34	0	0
Chronic pulmonary aspergillosis	34	1	3
Cryptococcosis	34	0	0
Histoplasmosis	34	0	0
Hypersensitivity pneumonitis	23	2	9
Interstitial lung disease	23	2	9
Pneumoconiosis	23	1	4
Thoracic malignancy	23	1	4
Pleural disease	23	5	22

N = number of study participants with relevant data available; n = number of participants displaying the relevant characteristic, symptom, or sign; PTB = pulmonary tuberculosis; TB = tuberculosis.

resolution of symptoms. Participants with persistent symptoms included nine (81%) of 11 diagnosed with bacterial pneumonia, four (50%) of eight diagnosed with bronchiectasis, one (100%) with chronic pulmonary aspergillosis, one (100%) diagnosed with pneumoconiosis, one (50%) of two with hypersensitivity pneumonitis, and one (50%) of two diagnosed with interstitial lung disease. Persistent symptoms included cough (13; 48%), dyspnea (7; 26%), night sweats (5; 19%), and hemoptysis (1; 4%). In those with in-person follow-up who had a physical examination, 13 (65%) had a lower BMI than at enrollment, and 11 (55%) had a reduced mid-upper arm circumference.

DISCUSSION

Despite routine use of sensitive molecular techniques to diagnose PTB in our setting, nearly half of patients were presumptively initiated on treatment of PTB without bacteriologic confirmation. In all but two participants in this group, we were unable to culture *M. tuberculosis* complex from induced sputum samples. In those in whom we could not bacteriologically confirm PTB, poor clinical outcomes including death, deteriorating mid-upper arm circumference, and persistent symptoms were the norm. Recent estimates are that mycobacterial culture of induced sputum has a sensitivity for PTB of 0.72 (95% CI, 0.66–0.77).²⁸ Therefore, it is likely that some participants in our study had PTB despite negative testing. However, we interpret our findings as strongly suggesting that diseases other than TB were causing many participants' symptoms. Using standard criteria, we diagnosed most patients with diseases that are neglected in national programmatic and WHO recommendations for PTB diagnosis and management.^{29–31}

We uncovered a broad range of diseases masquerading as PTB, but pneumonia and bronchiectasis were the most common. Bronchiectasis is a disease that reduces quality of life and causes hospitalization and death. Diagnosis has important implications for patients because it has specific treatments that improve quality of life and prognosis. The underappreciation of bronchiectasis in sub-Saharan Africa has long been recognized,¹³ but the relative lack of CT scanners, the primary diagnostic tool in well-resourced

healthcare systems, means it continues to be neglected for diagnosis and treatment. Although bronchiectasis can be caused by a range of underlying conditions, CT findings and the high prevalence of a past history of TB treatment suggested that prior TB may be the predominant cause in our cohort. There is increasing recognition of the persistent symptoms after PTB,³² and our study suggests differentiating post-PTB bronchiectasis from active PTB is challenging with available diagnostic tools.

We also identified a substantial proportion of participants with pulmonary consolidation and persistent symptoms indicative of bacterial pneumonia despite prior antibacterial drugs. Although radiographic consolidation may take several weeks to resolve after appropriate antimicrobial treatment, the persistence of symptoms may suggest unresolved infection. In this group, we identified a high prevalence of gram-negative bacteria in the sputum, particularly *Pseudomonas aeruginosa*, an organism usually resistant to commonly taken antibacterial medications, and *K. pneumoniae*.

An important finding is that although most participants in our study did not have bacteriologically confirmed PTB, presumptive treatment of their illness as PTB was supported by present national programmatic and WHO guidelines.^{29–31} Notably, almost all participants experienced symptoms compatible with PTB, had abnormal chest imaging, and continued to experience symptoms despite a course of antibacterial medication. Our study, in conjunction with other recent evidence, suggests limited specificity of clinical algorithms for the diagnosis of PTB.³³ The concerning clinical outcomes in our study of those in whom PTB was not confirmed may reflect the lack of treatment directed at the causative disease and highlight the impact of the limited specificity of current algorithms. Our findings suggest that for patients who test negative on Xpert MTB/RIF on adequate sputum samples the probability of PTB is low, and improved diagnostic pathways for patients who test negative on Xpert MTB/RIF are needed. Such pathways must be applicable at lower-level health centers and district hospitals and not exclusively PTB focused.

A strength of our study was a systematic approach that minimized bias. However, our diagnostic testing algorithm had limitations. Although mycobacterial culture of induced sputum is among the most sensitive diagnostic tests,³⁴ it is imperfectly sensitive and may have underestimated the prevalence of PTB. In addition, because our protocol did not include pleural sampling, TB may have been responsible for some of the pleural disease identified. Study limitations may have also altered the estimated prevalence of non-TB diagnoses. Some conditions, particularly cardiac or renal conditions that cause dyspnea and cough, cannot be adequately diagnosed with microbiological and radiographic testing. For some diseases, such as bacterial pneumonia, our definition may include patients with noninfective causes of consolidation. In addition, we did not test for every potential pathogen. *Pneumocystis jiroveci* is one notable example, an important TB mimic among HIV-infected individuals.¹⁵ Similarly, the use of standard media for sputum culture may underestimate the contribution of *Burkholderia* species and *Legionella* species, and the high prevalence of antibacterial use may have influenced the success of bacterial isolation. For other diseases, for example malignancies, the definitive test, histological examination of lung tissue, was not performed.

We recruited approximately two-thirds of those eligible, with critical illness the primary reason for exclusion, and the causes of illness in the critically unwell may differ. The patients enrolled in our study are broadly typical of those beginning treatment in Tanzania. Data from the Tanzanian electronic TB register show participants in our study had an approximately 10-year older median age but otherwise had very similar demographic characteristics, bacterial confirmation prevalence, and mortality to the contemporaneous national cohort.¹⁶ An analysis of this national dataset identified lack of bacterial confirmation as an independent risk factor for all-cause mortality.¹⁶ One important feature of our cohort is that the HIV prevalence was approximately half of that seen in the national TB registry. Because patients with HIV are less likely to have TB confirmed bacteriologically and are more likely to die of their disease,³⁵ our findings should be interpreted cautiously in patients with HIV infection.

In conclusion, our study highlights the importance of diseases that mimic TB in patients beginning treatment of PTB. Our study is from a single region in Tanzania, has a small sample size, and has focused on respiratory and infectious mimics of PTB. Therefore, replication of our work in other settings, in larger cohorts and including diagnostic testing for cardiac and renal disease, is warranted.

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