Community determinants of health care seeking for tuberculosis: The role of socio-cultural determinants and gender in Tanzania

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Grace Mhalu

aus Tansania

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Abbreviations

AIDS	Acquired Immune Deficiency Syndrome
aoR	adjusted odds ration
CI	Confidence Interval
DOT	Directly Observed Therapy
DOTS	Directly Observed Therapy Short course
EMIC	Explanatory model interview catalogue
EPTB	Extrapulmonary tuberculosis
GIS	Geographical Information system
GPS	Geographical Positioning System
HIV	Human immune deficiency virus
IQR	Interquartile range
IHI	Ifakara Health Institute
IRB	Institutional Review Board
LMIC	Lower-middle income countries
LDFU	Loss to diagnostic follow-up
LTFU	Loss to follow-up
MDH	Management Development Health
MTB	*Mycobacterium tuberculosis*
MTB	Multi-drug Resistant TB
NIMR	National Institute for Medical Research
NTLP	National Tuberculosis and Leprosy Programme
ODK	Open Data Kit

OR	Odds ratio
SDH	Social Determinants of Health
TB	Tuberculosis
TP	Traditional Practitioner
TZS	Tanzania shilling
TH	Traditional healer
USD	United States Dollar
USA	United States of America
UN	United Nations
WHO	World Health organization
X-DR TB	Extensively Drug Resistance TB

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Summary

The WHO End TB strategy targets to end the global tuberculosis epidemic by 2035 with a reduction of 90% new cases, a 95% reduction in deaths, and to ensure that no family is burdened by catastrophic costs as a result of tuberculosis. In order to reach this ambitious goal, not only strengthening of tuberculosis control programs, discovery, development and evaluation of novel and sensitive tuberculosis diagnostics tools will be required, but also actions with regard to social determinants of tuberculosis and health care seeking, particularly in low-income settings with high tuberculosis burden. Furthermore, novel and more sensitive TB diagnostics tools will only have an impact at the population-level if the millions of undiagnosed TB cases reach health care centres timely for diagnosis and treatment. The low tuberculosis case detection observed in Tanzania and elsewhere is not only due to limitations in tuberculosis diagnostics, but also in the socio-cultural and economic factors which are relevant for tuberculosis healthcare seeking, timely diagnosis and treatment.

This doctoral thesis therefore aimed to assess the pathways and costs of care from the onset of tuberculosis symptoms, to explain patient and diagnostic delays and loss to diagnostic follow-up during health care seeking, and finally to explore the role of traditional healers in tuberculosis management and control in Tanzania, using quantitative and qualitative methods. It firstly makes use of data obtained from the on-going tuberculosis cohort study in Dar es Salaam Tanzania, interviewing 100 confirmed and 100 presumptive tuberculosis patients on pathways to care and on direct and indirect costs, with data recording on tablets using the OpenDataKit (ODK) application. Secondly, data were collected during an intervention study on intensified case findings at pharmacies in Tanzania, administering a semi-structured explanatory model interview based on the EMIC framework for cultural epidemiology

to 136 presumptive and confirmed TB patients. It further used data from in-depth interviews and structured interviews with 90 traditional healers in urban, peri-urban and rural districts of Tanzania.

Pathways to care in confirmed tuberculosis patients were complex compared to the presumptive patients. In confirmed patients, pathways involved several visits to health care facilities before diagnosis, while that of the presumptive patients were more direct with only one or few visits to healthcare facilities before diagnosis. Confirmed and presumptive TB patients spent a median of 31% of their monthly household income on health expenditure for all five visits to healthcare facilities. Indirect costs were considerably higher than direct costs both in confirmed and presumptive TB patients.

A patient delay of ≥3 weeks was observed in almost two thirds of our participants from the intervention study. In addition, loss to diagnostic follow-up was observed in 44.1%. Prior consultations with traditional healers were associated with patient delay but not with loss to diagnostic follow-up. Gender differences were observed in patient delay and LDFU, whereby the odds of patient delay were higher in females than in males, and also loss to diagnostic follow-up was higher in females than in males.

Knowledge on cough and tuberculosis related symptoms was limited among traditional healers and varied in urban, peri-urban and the rural settings. Costs spent for traditional healers for treatment of cough and tuberculosis symptoms were lower than costs incurred by patients from the formal healthcare providers. Traditional healers in all three study sites referred patients for further treatment. Collaboration among the traditional healers, the government (NTLP) and other stakeholders was

limited. There was a significant association between collaboration with the government and referring patients to hospitals for further treatment.

The results from this PhD project contribute to our understanding on the pathways and costs of care in confirmed and presumptive tuberculosis patients. This study is among a few to report costs associated with tuberculosis taking onto account gender differences and poverty status. Furthermore, it contributes to open questions regarding patient delay and loss to diagnostic follow-up during healthcare seeking. Our study is also among the few to address the gap on the role of traditional healers in tuberculosis management particularly from sub-Sahara Africa. Given the importance of tuberculosis in terms of global disease burden, and the WHO's ambitious goal to end tuberculosis by 2035, planning and specific interventions which integrate social and biomedical solutions are needed.

Introduction

1.1 Tuberculosis

1.1.1 A short overview of the disease, its diagnosis and treatment

Tuberculosis (TB) is an airborne disease caused by bacillus *Mycobacterium tuberculosis* (*M.tuberculosis).* The bacillus may infect the lungs causing pulmonary TB or it might infect other sites such as lymph nodes, bones, and joints leading to extrapulmonary TB (EPTB) (Dye C, 2015; WHO, 2016). The bacteria are carried through airborne particles (droplets nuclei) and they can remain in the air for several hours depending on the environment. Transmission occurs when a person inhales the bacillus from an infected individual with active pulmonary TB through sneezing, coughing, shouting or talking (Dye C, 2015).

Risk factors for TB include those associated with exposure to the infectious nuclei droplets such as overcrowded environment and migration of individuals from a low incidence to an area of high incidence of TB or vice versa (Lienhardt C, 2001) and those associated with impaired host immunity as HIV-co infections, furthermore with co-morbidities such as diabetes, malnutrition, and with behavioral factors such as alcohol abuse as well smoking (Shanmuganathan and Shanmuganathan, 2015).

Diagnostic tests for TB include molecular tests, sputum smear microscopy and culture. Among the molecular tests, Xpert® MTB/RIF assay (Cepheid, USA) is the currently recommended test by WHO (WHO, 2017). The assay requires minimal technical training to be run, results are available within a short time and the test identifies possible multi-drug resistance TB (Center for Disease Control: Division of tuberculosis elimination, 2013). Sputum smear microscopy is less sensitive and specific compared to the Xpert® MTB/RIF assay (Orina et al., 2017). The culture-

based method requires more developed laboratory capacities and it can take up to twelve weeks to obtain the results (Kadioglu et al., 2014).

TB treatment involves a combination of several antibiotics. The standard treatment regime for new patients with pulmonary TB includes a six-month regime with two months of initial treatment, followed by a continuation phase of four months. During the initial phase, patients receive a combination of isoniazid, rifampicin, pyrazinamide and ethambutol (2HRZE), and isoniazid and rifampicin in the continuation phase (4HR) (WHO, 2010a).

1.1.2 Global burden of disease

Globally, TB is one of the top ten causes of death and a leading cause from single infectious agent ranking above HIV/AIDS (WHO, 2017). Furthermore, TB ranks among the top three causes of global burden of disease (GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, 2018). In 2017, there were 1.3 million deaths among Human Immunodeficiency Virus (HIV) negative people, and 10 million new TB cases occurred of which 64% among males (WHO, 2018). Additionally, TB is the single most common cause of death in HIV-infected individuals (WHO, 2015a). TB continues to mark as a public health problem particularly in resource-constrained settings despite the advancement in biomedical achievement of effective chemotherapy and prophylaxis (WHO, 2017). A recent United Nations general assembly high-level meeting on TB endorsed an ambitious declaration to accelerate progress towards ending TB (United Nations, 2018). It also emphasized that current global actions and investments on TB are not enough to end the global epidemic.

TB global burden of disease is also mostly caused by multi-drug resistant TB (MDR TB) as well as extensive drug-resistant TB (X-DR) TB. WHO estimates that 600,000 people were infected with MDR-TB in 2016 (WHO, 2017). Since MDR-TB and X-DR

TB are highly expensive to treat and require prolonged treatment duration, they contribute substantially to the global burden of disease (Nathanson et al., 2006).

TB burden in Africa is estimated to be higher compared to other regions due to the HIV epidemic (Chaisson and Martinson, 2008). In 2017, 9% of all people affected by TB globally were people living with HIV of which 72% were in Africa (WHO, 2018). Furthermore, the current estimates of the global burden of TB from Africa may represent an underestimate of the actual burden since they are based on calculations from reported notification data and expert's opinions (WHO, 2016). The actual magnitude of the problem in Africa remains undefined due to poor diagnostic infrastructures, reporting, and recording systems. The high burden in Africa is also partly caused by weak healthcare systems, suboptimal laboratories and further conditions which increase TB transmission such as overcrowding (WHO, 2015a, 2016).

1.1.3 TB in Tanzania

With a prevalence of 295 cases per 100,000 in the adult population, Tanzania remains among the 30 countries with a high burden of TB (Ministry of Health and Social Welfare, 2013a; WHO, 2018). A total of 65,902 cases of all forms were notified in 2016 which is an increase of 5.6% compared to 2015 (Ministry of Health and Social Welfare, 2016a). TB notification rates were higher in males than females by 61%, translating into a sex ratio above 1:1.5. The highest number of cases notified was observed in the age groups of 25-34 and 35-44 years for both females and males.

The Dar es Salaam region has the highest notification rates, accounting for 20% of all cases notified in Tanzania (Ministry of Health and Social Welfare, 2015, 2016a). Additionally, based on passive routine case detection (i.e. individuals with TB

symptoms present themselves in a healthcare facility for diagnostic services), it is estimated that until 2015 the case notification rate was below 50% in Tanzania, pointing to a substantial under detection (Ministry of Health and Social Welfare, 2013a).

Diagnosis of TB in Tanzania is primarily based on sputum microscopy; however, the use of GeneXpert MTB/RIF assay (Cepheid, CA, USA) is becoming a widespread technology. In 2016, a total of 71 healthcare facilities used GeneXpert machines (if there was no shortage), and the country average utilization was 35% (Ministry of Health and Social Welfare, 2016a).

Treatment success rates in 2016 were 90%, which is an improvement of about 80% compared to 2001. Likewise, the death rate has been declining from 8% in 2006 to 6% in 2014 (Ministry of Health and Social Welfare, 2016a). The high success rates result from an early adaptation and implementation of the directly observed treatment short course (DOTS) strategy (Egwaga et al., 2009; WHO, 2010a).

1.2 Determinants of TB

1.2.1. Socio-cultural determinants of TB

The way a society is constructed exposes certain populations more often to higher risks of TB infection, greater chances of developing active TB, and lower likelihood of accessing effective TB treatment (Mason PH, Degeling C, 2015). Furthermore, the way people perceive and act towards TB is shaped by social and cultural factors.

According to WHO, social determinants of health (SDH) originate from structural determinants of health which are conditions that reinforce the stratification of individuals into different social positions (classes). This stratification of individuals is based on individuals' income, gender, race, ethnicity, education as well as occupation. The social positions in turn shape specific determinants of health among

the individuals. Subsequently, individuals experience differences in exposure and vulnerabilities to health-compromising conditions (WHO, 2010b). Social stratification thereby leads to an unequal distribution of SDH such as: living conditions, behavioural and biological factors (WHO, 2010b).

Figure 1 displays the structural and social determinants of TB. The key structural determinants of TB epidemiology include: global socio-economic inequalities, rapid urbanization, population growth and increased mobility. These conditions enhance social determinants of TB, such as poor housing conditions, environmental conditions, financial and geographic problems, malnutrition as well as cultural barriers to health care access. In turn, the population distribution of TB reflects these social determinants that has an impact on TB pathogenesis from the exposure to infection, to diagnosis and treatment (Hargreaves et al., 2011; Lönnroth et al., 2009).

Socio-cultural determinants of TB are among the key risk factors for TB. For example, overcrowding in workplaces or homes and poor housing conditions increase the likelihood of an exposure to TB infection (Lienhardt C, 2001). Social, economic and cultural as well as geographical factors substantially contribute to barriers to successful case detection and TB treatment (Mason PH, Degeling C, 2015). For example, TB patients in Ethiopia could not start TB treatment on time due to long travelling time and financial burdens (Tadesse et al., 2013a).

The socio-cultural determinants of TB are not solely responsible for the persistence of TB as a global public health problem. Unmet social challenges as part of social-cultural determinants are crucial also for TB control (Rubel, 1992). Therefore, beyond understanding of the biology of infection and health systems' performance, a better understanding of the socio-cultural context that affects illness and behaviour of people with TB is needed (Weiss MG, Sommerfled J, Uplikar MW, 2008).

Solutions for the effective control and treatment so far have largely relied on biomedical approaches and neglected socio-cultural approaches. A more comprehensive strategy with bio-socio-cultural approaches is needed for an effective TB control (Wingfield et al., 2018)

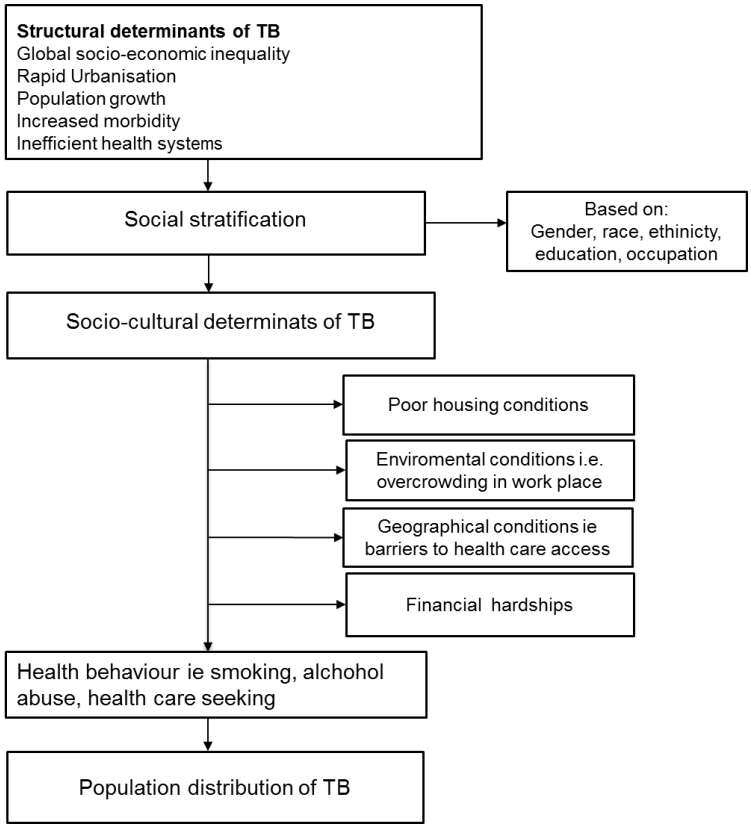

Figure 1: Structural and social determinants of TB

1.2.2 Socio-cultural determinants of TB in Tanzania

In Tanzania, the different prevalence rates of TB have been observed. It was, for example, estimated to be higher in the mainland compared to Tanzania Island (Ministry of Health and Social Welfare, 2013a). Tuberculosis notification rates in Dar es Salaam were the highest (244 cases per 100,000 population) in the country, while Kigoma and Unguja had the lowest notification rates of less than 50 cases per 100,000 population (Ministry of Health and Social Welfare, 2016a). Though these notification rates might be attributable to biological factors, social constructions of

these societies might also have a substantial effect on the notification rates. For example, in communities where people live in overcrowded conditions, and one of the member of the household has TB, we would expect higher TB notification rates. Therefore, biological factors are not only associated with high notification rates, but also social constructions of the societies such as overcrowding. Likewise, the clinical characteristics and helminth co-infections differed among TB patients in the rural and urban settings of Tanzania (Sikalengo *et al.*, 2018). These two examples underscore that not only the biological and genetic differences play a role for TB susceptibility, but also the social constructions and the physical environment.

A recent study from Tanzania showed that ideas about the spread of TB and its association with HIV/AIDS led to the stigmatization among TB patients (Miller et al., 2017). The effects of stigma may lead to social discrimination, subsequently adversely affecting health care seeking of an individual, and consequently the treatment outcomes (Miller et al., 2017). Furthermore, cultural understandings and perceptions of the individuals sometimes explicitly influence the health-seeking behaviour of the individuals. As (Bussey-Jones and Genao, 2003) found, understanding the individual perceptions led to effective treatment and eventually positive treatment outcomes.

Another study from Tanzania indicated that individuals with no employment delayed seeking health care more than those who were employed (Mfinanga and Mutayoba, 2008a). This clearly indicates the social determinants of TB as financial hardship may influence the health care seeking of the individuals.

1. 3 Health care seeking behaviour

1.3.1. Health care seeking behaviour and pathways to care

Health care seeking behaviour is largely determined by underlying social and cultural practices, the socio-economic status and access to health care (Zyaambo et al., 2012). Socio-cultural aspects are key factors in understanding health-seeking behaviour since TB transmission and progression are also driven by social factors (Ali, 2014; Ortblad et al., 2015).

Globally, about 4 million people are estimated to be missed each year by health systems and therefore, many do not get the required health care (WHO, 2017). This might furthermore result from seeking health care at facilities with inadequate TB diagnostics (dispensaries, pharmacies and traditional healers) which actually is common for the health care seeking behaviour of the majority of people in resource-limited settings (Senkoro et al., 2015a; Ukwaja et al., 2013a). Consequently, this leads to on-going transmission in resource-limited settings like Tanzania.

The main strategy for the identification of TB cases in Tanzania largely depends on passive case findings (patient presenting themselves to TB clinics to seek health care) (Ministry of Health and Social Welfare, 2013b). Thus, case finding largely depends on patient motivation, knowledge in seeking care, and effectiveness of diagnostic services (Dujardin and Kegels, 1997).

There is a significant association between levels of education and the knowledge about TB and health care seeking behaviour from onset of symptoms. Patients who could not recognize symptoms such as chest pain and night sweats sought care less than those who could recognize such symptoms. Likewise, patients who had an education background below primary education sought care less than those with

primary education and above (Mfinanga and Mutayoba, 2008a; Eliud R. Wandwalo and Mørkve, 2000a). Moreover, inequalities in income and access to resources have also been documented as factors determining the health care seeking behaviour of individuals in resource-limited settings. Results from a recent prevalence survey in Tanzania and results from a study in Zimbabwe indicated that lack of money was a factor associated with not seeking care (Senkoro et al., 2015a; Zyaambo et al., 2012).

Presumptive TB patients (coughing for more than two weeks), particularly from low-income groups, have long and complex pathways to care. Initiated care for presumptive TB patients often starts in the private sector and the consultation of three to four care providers before reaching public sector (Said et al., 2017; Shete P.B et al., 2015). Complex pathways to care result in treatment delay and therefore contribute to worsening patient morbidity and mortality.

1.3.2 Health care utilization in relation to health care seeking

The conceptual framework for access to medical care by Andersen (Aday and Andersen, 1974) is used for this study and modified for the context of health care seeking for TB patients. The model has been conceptualized, proceeding from the health policy in relation to the characteristics of population at risk and the health delivery system (Figure 2.)

Health policy is the entry point to the access and healthcare utilization. Health policy affects the access and utilization of healthcare services and has a direct relationship with the population at risk and the health delivery system. The health delivery system is characterized by two elements i.e. resources and organization. Resources include labour and capital involved in healthcare. Organization entails what the system does

with its resources, how the physicians and the health facilities are organized for healthcare utilization.

For this PhD project, we focus on the population at risk (red box) in relation to the utilization of health care services and consumer satisfaction (red arrows). The characteristics of the population at risk are defined as the function of three elements including: pre-disposing factors, enabling factors and need factors. It describes how people`s use of health services are a function of their predisposition (i.e. their characteristics). Use further depends on the consumer satisfaction and the utilization of health services. Consumer satisfaction refers to the attitudes of the population at risk towards care that they have received in terms of quantity and quality. Satisfaction also include: the convenience, costs and coordination. Healthcare utilization has also a direct relationship with the population at risk.

The components of utilization include the type of health care received and who provided care (example: traditional healer or physician or pharmacist) to the population at risk. It further includes the site where the service was provided (example: in hospital or at the pharmacy) and the time interval for the visit to the healthcare provider. We explain in detail the three elements of the population at risk and draw examples from healthcare seeking in TB.

Predisposing factors:

Predisposing factors describe the propensity of individuals to use the health services based on factors existing prior to the onset of illness (Aday and Andersen, 1974). They include demographic characteristics of the individual such as: age, sex/gender, education, occupation, social relationships social compositions, and health beliefs (e.g. knowledge related to health and health services) (Babitsch et al., 2012). Evidence suggests for example that there is a significant association between gender and health care utilization particularly for TB. Women tend to seek health care less frequently than men and use healthcare providers with sub-optimal or no adequate diagnostic equipment (Eastwood and Hill, 2004a; Krishnan et al., 2014; WHO, 2006). These factors are classified as predisposing factors that can shape the health seeking behaviour of individuals as well as healthcare utilization.

The need factors:

Need factors refer to the illness level which is the immediate cause to use services, and may be perceived by the individual or health delivery system (Aday and Andersen, 1974). The model differentiates between the perceived need for health care services (i.e., how people view and experience their general health, and illness symptoms) and the evaluated need (the professionals' assessment and diagnosis of patient's health status) (Aday and Andersen, 1974; Babitsch et al., 2012). Need factors have been shown to account for the differences in health seeking and healthcare utilization. In a study from Argentina, individual's utilization of health care services depended on whether they perceived their general health to be poor or good. Patients with increased age had the largest associations with utilization of health services compared to those in middle and reproductive age (Jahangir et al., 2012). Furthermore, in Tanzania individuals with additional symptoms other than

cough and haemoptysis sought health care, seeking twice as much compared to those with no additional symptoms (Senkoro et al., 2015a). Moreover, perceiving TB services as being free, doubled the chance of health care seeking in Angola (Luis et al., 2011).

Enabling factors

Enabling factors describe the means available for the individuals to use health services. These include both the individual resources and the attributes of the community in which the individual lives for example in a rural or in an urban area (Aday and Andersen, 1974). Individual resources include the individual's income and wealth to pay for the health services, while the community or organizational factors include resources for healthcare available in the community such as: travel time, means of transport and waiting time for health care (Babitsch et al., 2012). Associations have been found between financial capabilities or individual’s income and health care utilization in TB. In Nigeria for example, individuals utilized traditional healers (THs) more frequently than any other health provider because the costs of care were cheaper compared to other healthcare facilities (Christopher and Bosede, 2010).

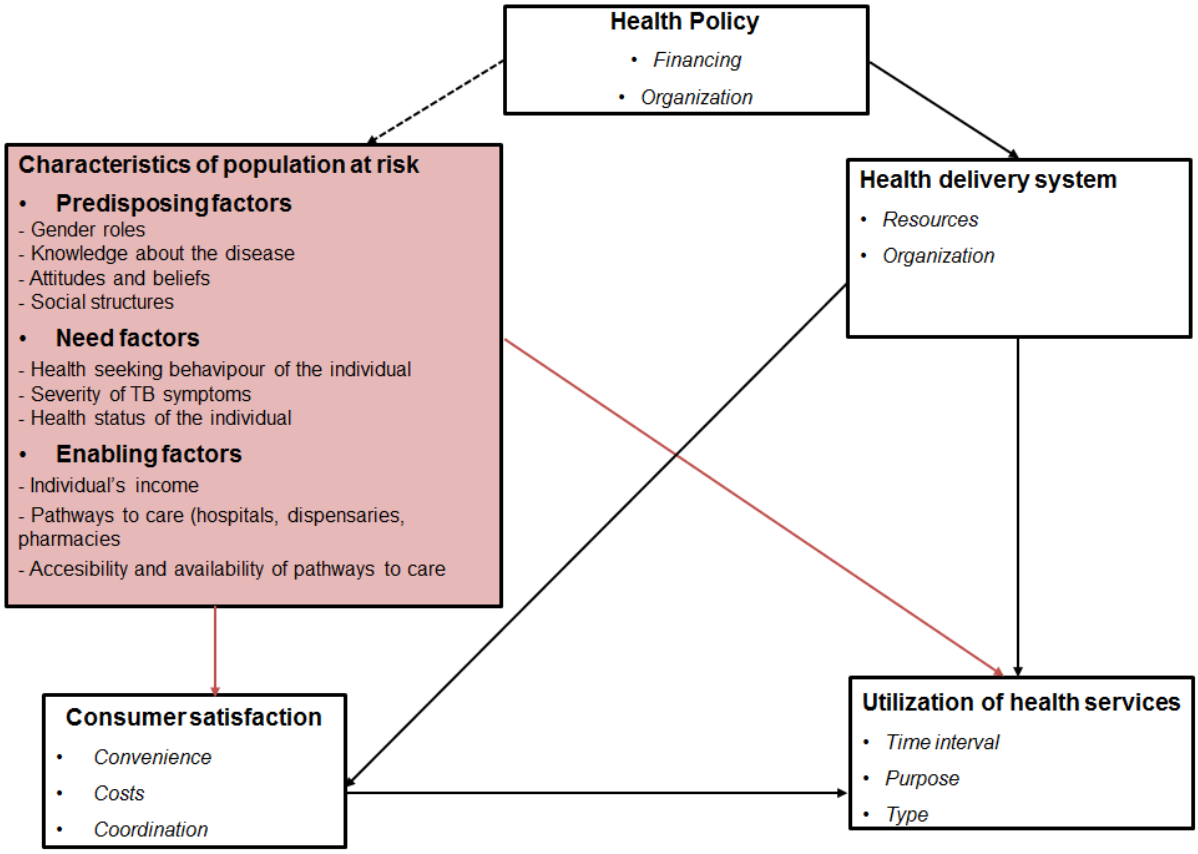

Figure 2. Conceptual framework for health care utilization (red box, red arrows) in relation to the theoretical framework of access to health care by (Aday and Andersen, 1974)

1.4 Healthcare seeking for TB and loss to follow-up in TB

Early diagnosis and efficacious treatment are important factors for effective TB control (WHO, 2009). Timely healthcare seeking is crucial because an untreated TB patient can infect an average of 10 contacts annually and more than 20 during the natural history of disease until death (Dye C, 2015). Health or healthcare seeking behavior has been defined as 'any action undertaken by individuals who perceive themselves to have a health problem or to be ill for the purpose of finding an appropriate remedy (Olenja, 2003). Healthcare seeking is preceded by a decision making process influenced by cognitive factors of the individual, by household behaviour and furthermore by community norms and expectations. Also, provider-

related characteristics and contextual factors such as availability of services and health costs are playing a role, as elaborated by (Olenja 2003). Healthcare seeking involves recognition of symptoms, perceived nature of illness, eventually relying on home care in a first step, eventually followed by seeking care at a health facility. The final choice of a healthcare seeking option is seen as interplay of these factors. It furthermore involves also eventual returns to a health facility in case of treatment failure, or seeking care at an alternative care provider.

In this thesis, we focus on two components of healthcare seeking: Delay in healthcare seeking and loss to follow-up until TB treatment.

1.5 Delay in healthcare seeking for TB

Delay durations have been defined and categorized differently (Sreeramareddy C.T, Panduru K.V, Menten J, Ende J.V, 2009a; Storla et al., 2008; WHO, 2009). WHO defines patient delay as the interval between the onset of symptoms and the first presentation to the healthcare provider (Figure 3) (WHO, 2009). Diagnostic delay is the interval between the onset of symptoms and diagnosing the patient as a TB patient (Sreeramareddy CT, Oin ZZ, Satyanarayana S, Subbaraman R, 2014; Yimer et al., 2005). Treatment delay on the other hand is the time interval between tuberculosis diagnosis and initiation of anti-TB treatment (WHO, 2009). Total delay defined as the time interval from the onset of TB symptoms until initiation of anti-TB drugs. It is the sum of patient delay, diagnostic delay and treatment delay (WHO, 2009).

Delay in seeking care is more pronounced in females than in males (Mfinanga and Mutayoba, 2008a; Pronyk et al., 2001; Storla et al., 2008). On average, the delay before seeking care is eight weeks among women compared to six weeks among men (World Health Organization, 2009). This is mainly influenced by women

primarily being the family caregiver and the lack of financial autonomy. One of the reasons for lack of financial autonomy among women is mostly attributed to women remaining at home to take care of their families while men work outside the homes and can provide economic substance to the families. Furthermore, stigma also plays a major role in shaping the perception of illness and help-seeking behaviour among women. As women are dependent on their families or spouses, they are always concerned about the social isolation and marital problems that may arise as an impact of TB i.e. divorce (Onifade et al., 2010; Somma et al., 2008a; Weiss et al., 2008a).

Several factors have been identified to influence delay in diagnosis until treatment initiation including: patient knowledge and perception of the causes of disease, older age and stigma (Auer et al., 2000a; Ngadaya et al., 2008a; WHO, 2009), distance between the patient's household and the healthcare facility, socio-economic level of the patient, severity of the disease and health facility capacities such as the availability of the healthcare personnel (Cai et al., 2015; Mfinanga and Mutayoba, 2008a).

Delay of treatment is said to be influenced furthermore by the degree of diagnostic suspicion from the physician as well as effective diagnostic services (Dujardin and Kegels, 1997). While all these factors are crucial in the TB control and management, there are always setbacks by delays either with the patient or with the healthcare system (the time interval from the first contact with the healthcare services until the date of diagnosis) (Sreeramareddy C.T, Panduru K.V, Menten J, Ende J.V, 2009a).

Delays in TB diagnosis and treatment initiation are not only important prognostic factors for poor clinical outcomes, but are also a major public health concern because undiagnosed infectious TB patients continue to transmit TB to their

household contacts and the community (Sreeramareddy CT, Oin ZZ, Satyanarayana S, Subbaraman R, 2014; Yimer et al., 2005). Delay in seeking care may negatively impact the decline in TB transmission, which is a crucial factor to meet the ambitious WHO targets of TB control and elimination.

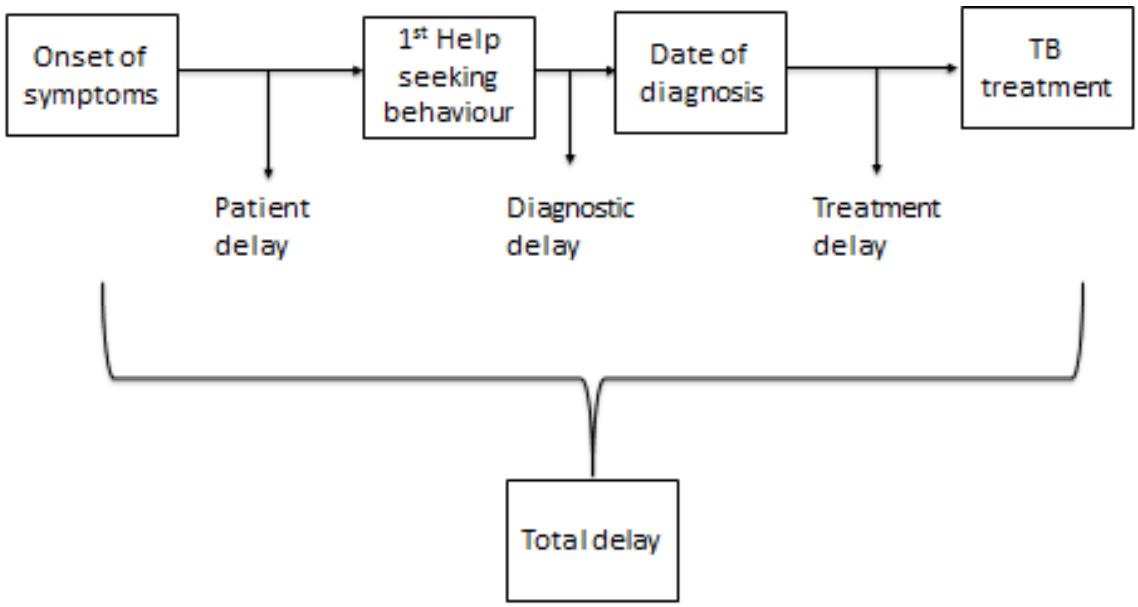

Figure 3. Schematic overview of different delay durations contributing to the total delay in health care seeking (Adopted and modified from WHO-TDR diagnostic delay in TB)

1.6 Loss to follow-up in TB

The care pathway for presumptive and TB patients starts with the identification of the symptoms that lead to seeking health care. Individuals may drop out of care if they are not identified as tuberculosis patient, during diagnosis (i.e. loss to diagnostic follow-up, LDFU), before treatment initiation (pre-treatment loss to follow-up) or during treatment (i.e. loss to follow-up, LTFU) as shown in figure 4 (MacPherson et al., 2014a). Any loss along this pathway poses a great challenge in TB control as high mortality rates are reported in this group as was found in South Africa with loss of smear-positive patients where mortality rates were substantial (Botha et al., 2008; Squire et al., 2005). Furthermore, case identification of smear-positive patients and

prompt treatment initiation are key factors in TB control (Dye et al., 2008). These two approaches are promoted as parts of DOTS passive case finding by WHO (WHO, 2010a).

Several factors have been found to have a direct association with LTFU during the diagnostic process or during treatment, falling into two categories: those related to the patient and those related to the health system. Factors such as male sex, and older age (Gopi et al., 2005a), living in rural residence, perception that TB is associated with HIV/AIDS and financial hardships were found to contribute to LTFU (Ade et al., 2016; Buu et al., 2003a; Muture et al., 2011).

Health system related obstacles include dissatisfaction with long waiting time during diagnosis and treatment and inappropriate handling of the presumptive or TB patients by the healthcare workers. For example, even after recognising the symptoms to be suggestive of TB, healthcare workers may refuse to take diagnostic measures (i.e, requesting of sputum samples), missing smear results, patient may not be informed by the clinic regarding the results as well as under diagnosis of the TB patients (Botha et al., 2008; Squire et al., 2005).

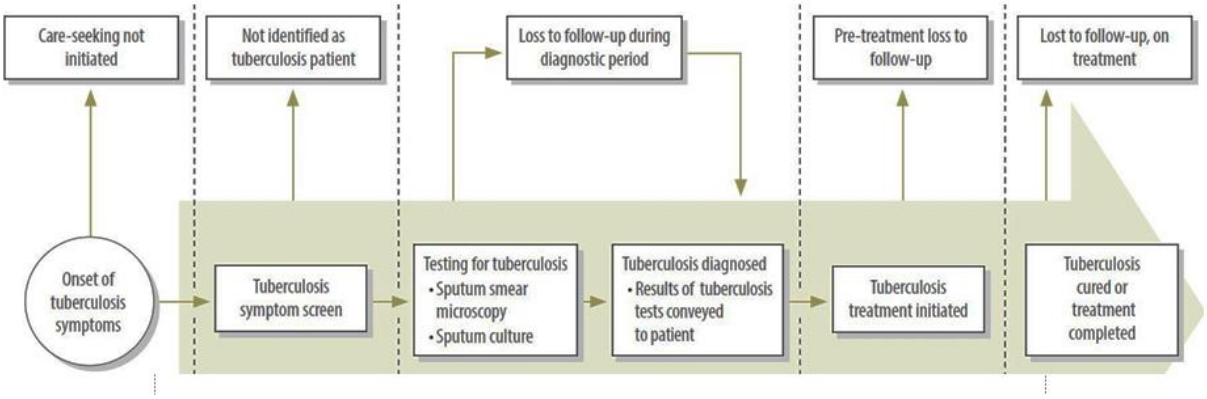

Figure 4. Schematic overview of pathway to care for TB patients, showing different episodes of loss to follow-up until TB treatment (MacPherson et al., 2014a)

1.7 TB and Gender

"Gender" refers to distinguishing features of males and females that are socially constructed (Uplekar et al., 2001). Gender is distinguished from "sex" as sex entails differences in men and women basing on their biological characteristics (WHO, 2005a). Gender affects TB epidemiology since the risk factors and health care seeking pathways for diagnosis and treatment are different among men and women (Mason et al., 2016). A cross-site analysis of gender and further socio-cultural determinants in India, Bangladesh and Malawi reported that gender influences the clinical presentation, illness-related experience, behaviour, and treatment outcomes (WHO, 2006).

1.7.1 TB in men and women

TB prevalence has been shown to be more than twice as high among men than among women in lower middle income countries (LMIC), with strong evidence that men are less seeking and/or accessing TB care in many settings (Horton et al, 2016). TB notification rates are also consistently higher in men than in women (Horton et al., 2016; WHO, 2017). The lower infection rates among women compared to men have been attributed to socio-cultural factors as women have less

social interactions outside the home compared to men. Although more TB cases and deaths occur among men worldwide, the burden of disease among women is high in countries with a high HIV prevalence (WHO, 2005a, 2014).

There is an on-going debate as to whether the higher notification rates in men stem from sex differences or from socio-cultural or gender differences (Mason 2017). It is unlikely that the pronounced variations in the male to female notification data in neighbouring countries such as Thailand and Vietnam are explained by biological reasons. Similarly, in a recent prevalence survey, the male to female ratio of notified TB patients in Tanzania was 1.4 (Ministry of Health and Social Welfare, 2013a), while that of Uganda stood at 1.2 (Ministry of Health Uganda, 2014). This difference could hardly be explained by biology. It may rather be due to variations in gender-related risk factors and gender-specific health seeking behaviours(Mason et al., 2017). As these differences are rarely accounted for in the epidemiology of TB, it is possible that sex differences in detection and reporting may be attributed to gender-specific barriers to health service utilization and diagnosis (Uplekar et al., 2001).

Evidence suggests that men and women interpret TB symptoms differently. In Vietnam, women reported cough and haemoptysis less frequently than men (Long et al., 2002). These differences remained significant even after controlling for variables as age, sex, family size and area of residence. Additionally, the general symptoms as tiredness, headache and fever were significantly more common in women than in men (Long et al., 2002). As documented elsewhere such variations may lead to clinicians missing out TB diagnosis in women as some may not request sputum examination as they request from men (Thorson et al., 2000a). Although these differences may partly be explained biological factors, socio-cultural factors also play a role. For example, sputum expectoration and coughing are culturally less

acceptable for women; therefore, women may expectorate less frequently than men, which may result in women producing less likely good quality sputum than men (Khan et al., 2004).

Furthermore, men tend to seek medical help more frequently after the onset of TB symptoms compared to women who tend to start treatment with home remedies or taking medicines without prescriptions before seeking professional help. Even when seeking medical help, women usually consult less qualified healthcare providers (Kaur et al., 2013; Weiss et al., 2008a). Both women and men face gender-specific barriers to TB diagnosis, care and treatment (Gosoniu et al., 2008a).

Adherence to TB treatment and treatment outcomes may also be affected by gender roles. Evidence suggests that women who are diagnosed and start TB treatment are more likely to adhere to treatment, have positive treatment outcomes and missed less the DOT appointment compared to men (Chan-Yeung et al., 2002).

1.7.2 Framework for the study of gender and TB

A stepwise attrition conceptual framework has been formulated to identify gender differentials at each step, as shown in the overview of the framework in figure 5 (Uplekar et al., 2001). Seven steps are proposed by the model, including awareness of symptoms, appropriate help-seeking, utilization of health services, diagnosis, treatment initiation, adherence to treatment as well as positive treatment outcomes. Gender differences may occur at each of these steps, from the onset of symptoms until treatment outcome.

The health care seeking behaviour of both men and women particularly for TB is largely determined by either how she or he and those around her perceive the symptoms, regard the diagnosis, accept the treatment and are ready to adhere to the treatment. The framework suggests that gender issues influence both the TB patient

and also the health care providers and thereby impact on the effectiveness of clinicians to diagnose TB while taking into account sex/gender differences.

The shortening double columns on the framework indicate the attrition that occurs as both men and women move through the various steps during healthcare seeking until TB treatment. For example, it has been documented that more men are diagnosed with TB, however, among those who receive treatment, more women adhere to the treatment regimen than men, have positive treatment outcomes and women die less often from the disease (Chan-Yeung et al., 2002; E Johansson et al., 1999).

The vertical lines indicate barriers during the process that may impair the effective efforts to achieve cure (Uplekar et al., 2001). Some of the barriers for cure may appear even before the help seeking, i.e. financial barriers for healthcare seeking that affect males and females differently. While males face financial barriers as a result of limited resources, females on the other hand lack financial autonomy that makes them dependent on their spouses and other family members, thereby limiting their access to care seeking (Krishnan et al., 2014). Furthermore, the barriers may continue even after cure, e.g. stigma that may be faced by both males and females. However, it has been documented that women usually report the burden of TB-related stigma more frequently than men and are afraid that their illness may result in marital problems, eventually leading to divorce and social isolation, even after cure (Karim et al., 2007; Krishnan et al., 2014). The horizontal arrows cutting through the barriers indicate the success pattern in overcoming the barriers.

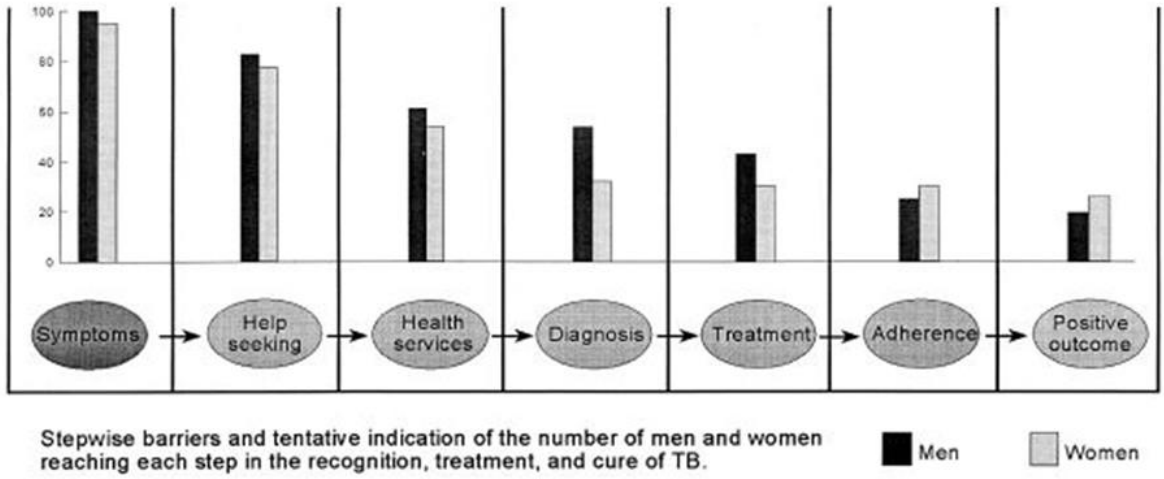

Figure 5. Framework for the study of gender and TB (adopted from Uplekar 2001)

1.8 Costs of TB care in relation to poverty and gender

TB is characterized as a result of poverty but also fuels poverty (Benatar and Upshur, 2010). People in resource-limited settings live in poor living conditions i.e. overcrowded houses with poor ventilation which play a major role in TB transmission (Lienhardt et al., 2003). Moreover other risk factors as malnutrition, smoking and alcohol abuse which are also characteristics of poverty are more prevalent in resource-limited settings. TB which accounts for a considerable global burden of diseases also leads to poor health that subsequently lower human productivity which in turn aggravates poverty. Universal access to healthcare and reducing the socio-economic burden of TB is therefore one of the key strategies proposed by WHO-Stop TB strategy for effective TB control (WHO, 2005b). Although access to free TB care has expanded substantially due to global and government efforts (WHO, 2017), TB patients in low and middle-income countries still face substantial costs as a result of TB (Onazi et al., 2015). Financial risk protection therefore remains a major issue on the way to a tuberculosis-free world, as stated by the Lancet Commission on tuberculosis (Goosby et al., 2018).

Despite the fact that TB treatment in most of the countries is provided for free, patients in low and middle-income countries still incur high direct and indirect costs that are catastrophic (Kemp et al., 2007; Ukwaja et al., 2013b). The onset of TB symptoms can exacerbate poverty as the patient enters into a lengthy period of healthcare expenditure and loss of productivity (Benatar and Upshur, 2010).

TB related costs may not only negatively impact the treatment outcome. High direct and indirect costs before and during TB treatment are also a reason why many of the TB affected households continue to fall more below the poverty line (Foster et al., 2015). Additionally, TB patients in resource-limited countries spend a substantial amount of their annual household income on TB treatment, particularly in the initial phase of health care seeking (Dye et al., 2009; Tanimura et al., 2014).

Costs for TB treatment are not uniform to all the patients (de Cuevas et al., 2016; Ramma et al., 2015): Men incurred higher direct costs and higher opportunity costs than women (Kemp et al., 2007). Though the costs of care for women seem to be low compared to those of the men, the opportunity costs faced by a household are always higher when women get sick compared to men, especially women in the reproductive years (WHO, 2014).

1.9 Traditional healers and TB

Traditional healers (THs) co-exist together with traditional medicine and are widely acknowledged worldwide. They are historically one among the widely used practices in the community (Mbwambo et al., 2007) and serve as the primary health care providers for a substantial proportion of individuals, especially in African communities (Gessler et al., 1995b). THs have been documented to treat a vast number of diseases including malaria, TB, diarrhea, sexually transmitted diseases and HIV/AIDS (Banerjee et al., 2000; Gessler et al., 1995b; Mbwambo et al., 2007).

Although THs are not a homogenous group, they serve as the entry point in health care seeking among a majority of people in sub-Saharan Africa (Eliud R. Wandwalo and Mørkve, 2000a; Wilkinson et al., 1999).

In sub-Saharan Africa, scant attention has been given to THs and their practices towards TB management. This neglect may lead to an increase in poor health outcomes and high mortality rates among patients who visit THs (Barker et al., 2006). For the diagnosis and treatment, THs use a broad range of different treatments such as plant roots, shoots and leaves. Diagnosis and treatment of TB and TB related symptoms are usually based on the patient's history and the cause of the disease (Banerjee et al., 2000).

It has been found that female patients visit THs more often than male patients. Strong traditional beliefs, the short time spent for visits to THs compared to visits at other healthcare facilities and confidentiality have been mentioned as the underlying reasons (Eastwood and Hill, 2004a).

1.10 Conclusion

In summary, TB is a major public health problem which contributes substantially to the global burden of disease. The socio-cultural determinants of TB are crucial factors that can significantly support the global efforts for effective TB control (Hargreaves et al., 2011). Gender roles influence the control that men and women have with regard to the determinants of their health, particularly for TB (WHO, 2005a). Gender also influences health-seeking behaviour from the onset of symptoms until treatment completion. Evidence shows that men are disadvantaged in seeking and accessing TB care (Horton et al, 2016), whereas women tend to visit health care providers that have sub-optimal or a lack of diagnostic equipment for TB as compared to men (Eastwood and Hill, 2004a). This subsequently leads to delays

in health care and treatment, increasing the period of TB infectivity in the communities. Additionally, the costs of care before and during TB treatment are higher for men than women whereas the opportunistic costs are more pronounced for women and their households (Kemp et al., 2007). This underscores the need to understand the cycle of TB patients, starting from the onset of symptoms, healthcare seeking, and access to health care services, until the end of treatment and post-TB treatment impairments.

2. Research Questions, Aims and Methods

2.1 Cohort study

Part of this PhD project was conducted within the framework of an on-going prospective cohort study in Dar es Salam Tanzania (TB-DAR). TB-DAR was initiated in 2013 with the overall goal of studying clinical and molecular epidemiology of TB in Tanzania. The cohort includes sputum smear positive or Xpert MTB/RIF positive TB patients, sputum smear negative or Xpert MTB/RIF negative patients (presumptive TB patients) and household contacts of the TB positive patients (household contact controls) (Mhimbira et al., 2017). The cohort is funded by Rudolf Geigy Foundation of Basel Switzerland, TB.

For the PhD project, an additional clinical record form with pathways and costs of care questions was integrated into the cohort database in 2016 and data were collected retrospectively in confirmed and presumptive TB patients. Ethical clearance was obtained from the Ifakara Health Institute Institutional Review Board, Coordinating Committee of the National Institute for Medical Research in Tanzania (NIMR), and Ethics Committee of the Canton of Basel (EKNZ).

2.2 Intervention study

The other part of the PhD work was conducted on the platform of an intervention study on intensified case findings at pharmacies (TB-PHARM). The overall objective was: to develop and evaluate a referral system of presumptive TB cases from pharmacies to National Tuberculosis and Leprosy (NTLP) TB clinics; to increase TB case detection; to reduce diagnosis delay; and to increase linkage to care (Mhimbira et al., 2015). The study undertook a systematic symptom screening for TB among pharmacy clients, and referral of the presumptive TB cases to the NTLP diagnostic

and treatment center (i.e. intervention center). Five pharmacies were selected based on the geographical location to the TB clinic, the ownership (government, private) and the size of the pharmacy. Additional data on LDFU was collected through a structured questionnaire for all patients who met the inclusion criteria of the LDFU study at the TB clinic after the referral from the pharmacies. Ethical clearance was obtained from the Ifakara Health Institute Institutional Review Board, Coordinating Committee of the National Institute for Medical Research in Tanzania (NIMR).

2.3 Research Questions & Hypothesis

As stated in the introduction section, solutions for effective TB control and treatment have largely relied on biomedical approaches and less is known on socio-cultural and gender differences and social determinants of TB. Furthermore, pathways to care and the costs of care during diagnosis for the confirmed and presumptive TB patients have insufficiently been addressed specifically in sub- Saharan Africa.

The PhD project aims to address three questions on socio-cultural determinants and gender issues in Tanzania. The questions include:

i) what are the pathways of care and costs of care among the confirmed and presumptive TB patients in Tanzania? Does cost of care before diagnosis in confirmed and presumptive TB patients differ among females and males?

ii) what role do socio-cultural aspects and gender have for LTFU while seeking care, and what are the reasons for LDFU on the pathway to care before TB diagnosis; and

iii) what is the role of THs in management of TB in Tanzania? Does the management of TB and cough related symptoms done by THs differ among the urban, peri-urban and rural settings of

Tanzania? Is there any collaboration among the healers and the government particularly on TB?

We hypothesize that gender and socio-cultural factors have an effect on health seeking behaviour of presumptive and confirmed TB cases, on costs of care before treatment initiation as well as on LTFU during the diagnostic period. We further hypothesize that THs play a role in healthcare of the confirmed and presumptive TB patients in urban, peri-urban and rural settings of Tanzania.

2.4 Aims

The PhD project specifically aims to:

1. Assess pathways and associated costs of seeking care from the onset of symptoms until TB diagnosis in confirmed and presumptive TB patients taking into account gender and poverty status

2 Study LTFU before TB diagnosis and its determinants (gender, socio-cultural factors) among presumptive TB cases in the community during an intervention study on intensified case finding; and

3. Explore the role of THs in TB control and management in comparison of urban, per-urban and rural Tanzania.

2.5 Methods

2.5.1 Study settings and study design

The study areas for the PhD project are described in details below (Figure 5). These included Temeke, an urban area (objective 1 and 3), Buguruni, an urban area (objective 2), Bagamoyo, a peri-urban area (part of objective 3), and Ifakara a rural area (part of objective 3).

2.5.1.1 Temeke district, Dar es Salaam (urban)

Temeke district is one among the three districts of Dar es Salaam, a business capital with approximately 5 million people and about 10% of the country's population (The United Republic of Tanzania, 2014a). Dar es Salaam region has the highest notification rates of TB, contributing 20% of all notified TB cases in the country (Ministry of Health and Social Welfare, 2016a). Temeke district is densely populated with a population of at least 1.4 million per person (The United Republic of Tanzania, 2013a). In 2016, 4,495 TB cases (all forms) were notified in the district (Ministry of Health and Social Welfare, 2016a).

2.5.1.2 Buguruni, Ilala district, Dar es Salaam (urban)

Buguruni is in the Ilala district of Dar es Salaam Tanzania, a metropolitan area with high TB burden. Ilala has a population of at least 1.3 million people with an average of 4.0 persons per household (The United Republic of Tanzania, 2013a). The study area was a residential area within the Buguruni sub-district with a population of 70,585 and 559 notified TB cases in 2012. The area is characterized with one registered TB diagnostic and treatment centre.

2.5.1.3 Bagamoyo, Pwani region (peri-urban)

The remaining part of the study was conducted in Bagamoyo. Bagamoyo is located in Pwani region of Tanzania. The region is characterized by few health care facilities and notifies < 5% of the TB cases per year (Ministry of Health and Social Welfare, 2016a; Tanzania National Bureau of Statistics, 2016a).

2.5.1.4 Ifakara, Morogoro region (rural)

Ifakara is located in the rural area of Kilombero district in the Morogoro region of Tanzania. The district is also characterized by few health care facilities and notified

about 5.4% TB cases in 2016 (Ministry of Health and Social Welfare, 2016a; Tanzania National Bureau of Statistics, 2016b).

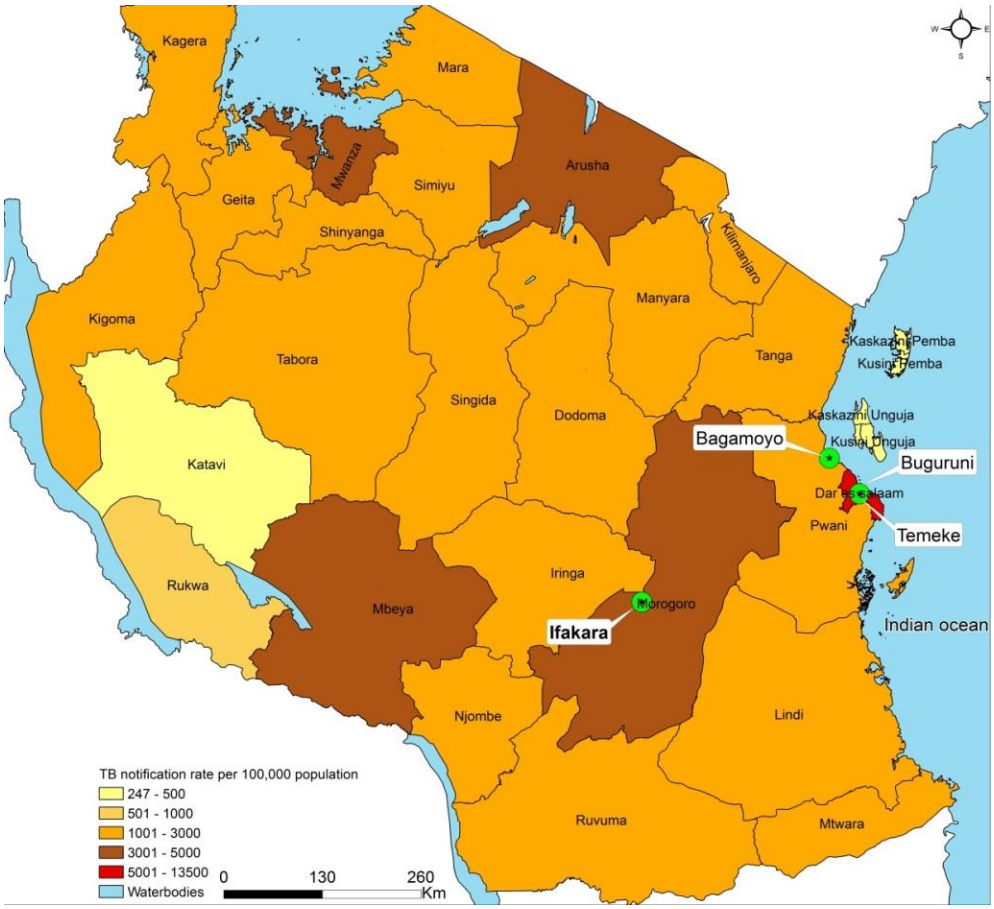

Figure 6. Study settings of the PhD project

2.5.1.5 Study design

We used a cross-sectional study design. For the first and second study objectives, we took advantage of the on-going cohort and intervention study on intensified case findings and conducted a survey among presumptive and confirmed TB cases. For our last objective, we conducted a survey in urban, peri-urban and rural settings of Tanzania.

2.6 Definition of main outcomes

2.6.1 Delay in seeking health care

Throughout the following chapters, we use the definitions of patient delay and diagnostic delay according to the framework of WHO on diagnostic and treatment delay (WHO, 2009). Diagnostic delay was defined as the interval between the onset of TB symptoms and the time of diagnosis of more than three weeks. Patient delay was defined as the interval from the onset of TB symptoms and consultation with the healthcare facility of more than three weeks. The interval of three weeks for both patient and diagnostic delay were considered sufficient based on previous studies (Said et al., 2017; Shete P.B et al., 2015).

2.6.2 Costs of care

Definitions for the direct and indirect costs of care were based on the WHO tool to estimate patient costs (WHO, 2008). Direct costs were defined as out of pocket costs linked to seeking diagnosis including medical expenses, transport, fees and food. Indirect costs were defined as the cost of foregone income due to inability to work and loss of time due to visits to health facilities.

2.6.3 LDFU

LDFU was defined as failure to present after referral from the recruitment pharmacy to the TB clinic (pharmacy LDFU) within two months, or failure to return for all three required diagnostic visits after recruitment in the TB clinic (clinic LDFU). More details on LDFU are described in chapter three.

2.7 Definition of exposures

2.7.1 Gender

In the quantitative analysis, gender was defined based on the self-report of being male/female, and the analytic approach included stratification by gender and by

poverty status. Furthermore, the analysis of the qualitative in-depth interviews paid attention to gender issues as an emerging theme. For further details on the definition see section 1.5.

2.7.2 Socio-cultural factors

We define patients as poor if their wealth fell in the lowest or second-lowest wealth quintile. The non-poor were defined as persons in the remaining middle, fourth and highest wealth quintiles as indicated in our first objective.

2.8 Statistical and qualitative analysis

The analytic approach for the three research questions are outlined below and described in detail in the respective papers of the result section.

Research question 1): What are the pathways of care and costs of care among the confirmed and presumptive TB patients in Tanzania? Does cost of care before diagnosis in confirmed and presumptive TB patients differ among females and males?

Pathways to care including the distance that confirmed and presumptive patients took and the costs of care were analysed by logistic regression as well as quintile regression models. All analyses were conducted using STATA version 14 (StataCorp College Station TX, USA). The specific covariates used and additional analyses are described in more details in chapter three.

Research question 2): What role do socio-cultural aspects and gender have for LTFU while seeking care, and what are the reasons for LDFU on the pathway to care before TB diagnosis.

LDFU and delay in seeking healthcare and their association with gender (chapter three) were analysed with univariate and multivariate logistic regressions. Variables of perceived causes of TB (i.e water, food, dust alchohol and smoking) and were first summarized by univariate statistics. Subsequently, multivariate logistic regression models were run for delay and LDFU.

To explain identified differences and associations of the variables delay and LDFU, we analysed narrative data. Narratives from the EMIC interviews were coded thematically and imported in MAXQDA version 12 (VERBI Software, Berlin, Germany). We further used the framework method of Gale to analyse the data.

Research question 3): What is the role of THs in management of TB in Tanzania? Does the management of TB and cough related symptoms done by THs differ among the urban, peri-urban and rural settings of Tanzania? Is there any collaboration among the healers and the government particularly on TB?

We used qualitative and quantitative approach to explore the role of THs healers. The qualitative analysis was preceded by verbatim transcription of the interviews. We developed codes that were checked for inter-coder-reliability and analysed the data focusing on emerging themes, patterns, similarities and differences. All qualitative analyses were performed using MAXQDA version 12 (Verbi Software, Berlin, Germany). We further performed quantitative analysis to assess THs knowledge on symptoms and causes of TB, traditional management of cough and TB related symptoms as well as distance from the TH to a near healthcare facility. We used chi square test of association to assess differences between groups All analyses were conducted using STATA version 14 (StataCorp College Station TX, USA).

2.9. Relevance of the research

Different patient pathways to care are an important part in recognition of public health interventions in TB control. So far, most studies have been focusing on patients who have already been diagnosed and on treatment, rather than the large presumptive population seeking care once they are aware of TB symptoms. Furthermore, studies on cost of TB have also predominantly focused on TB patients during TB treatment and little is known about cost of care not only before treatment initiation but also in presumptive TB patients (Shete P.B et al., 2015). Additionally, assessment of costs of care taking into account gender differences is understudied especially in sub- Saharan Africa. To our knowledge, the study by (Kemp et al.,

2007) is so far the only study that assessed cost of TB care taking into account gender differences and poverty status in sub-Saharan Africa. In this PhD project, we assess pathways and costs of care before TB treatment in confirmed and presumptive TB patients, taking into account gender differences and poverty status. Our study in chapter 3 contributes more on assessing costs of TB care before treatment initiation comparing the presumptive and confirmed TB patients.

Despite recent advances in molecular TB diagnostics such as Xpert MTB/RIF, the effect at population-level is relatively modest (Creswell et al., 2015) because presumptive TB patients do not reach the healthcare system on time for effective diagnosis and treatment. Studies on health seeking behaviour have predominantly focused on patients who have already been diagnosed within the health care system rather than presumptive cases with TB symptoms (Fatima et al., 2015a; Senkoro et al., 2015a). Novel and more sensitive TB diagnostics will only have an impact at the population-level if the undiagnosed TB cases reach health care centres in a timely manner for diagnosis and treatment (Creswell et al., 2015). This PhD project contributes to knowledge in this area where we investigate the reasons for patient delay, diagnostic delay and LDFU among the presumptive and confirmed TB patients in an urban setting of Tanzania.

Finally, It has been documented that most of the presumptive and TB patients in sub-Saharan Africa start treatment seeking from THs before reaching healthcare facilities for diagnosis and effective treatment (Brouwer et al., 1998; Wilkinson et al., 1999). However, the role of THs in TB management and control is largely unknown. Most of the studies on THs have only focused on how the patient utilizes services offered by a TH and not on how the THs manage TB patients. Therefore, there is a gap in addressing the role of THs particularly from sub-Saharan Africa. We again

contribute to the body of knowledge by assessing the role of THs in TB management in comparison of urban, peri-, urban and rural areas of Tanzania.

3. Pathways and associated costs of care in confirmed and presumptive tuberculosis patients in Tanzania: A cross-sectional study [1]

Grace Mhalu [1, 2, 3 *], Jerry Hella [1, 2, 3], Francis Mhimbira [1, 2, 3], Khadija Said [1, 2, 3], Thomas Mosabi [1], Yeromin P. Mlacha [1, 2, 3], Christian Schindler [2, 3], Sébastien Gagneux [2, 3], Klaus Reither [2, 3], Kees de Hoogh[2, 3], Mitchell G. Weiss [2, 3], Elisabeth Zemp [2, 3], Lukas Fenner [4 *]

[1] Ifakara Health Institute, Dar es Salaam Tanzania [2] Swiss Tropical and Public Health Institute [3] University of Basel, Basel, Switzerland [4] Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland

[1] Publication: BMJ Open: 10.1136/bmjopen-2018-02507

Abstract

Objective: To assess pathways and associated costs of seeking care from the onset of symptoms to diagnosis in confirmed and presumptive tuberculosis (TB) patients.

Design: Cross-sectional study.

Setting: District hospital in Dar es Salaam, Tanzania.

Participants: Bacteriologically confirmed TB and presumptive TB patients.

Primary and secondary outcome measures: We calculated distance in meters and visualized pathways to healthcare up to five visits for the current episode of sickness. Costs were described by medians and interquartile ranges (IQR), with comparisons by gender and poverty status.

Results: Of 100 confirmed and 100 presumptive TB patients, 44% of confirmed patients sought care first at pharmacies after the onset of symptoms, and 42% of presumptive patients did so at hospitals. The median visits made by confirmed patients was 2 (range 1-5), and 2 (range 1-3) by presumptive patients. Patients spent a median of 31% of their monthly household income on health expenditures for all visits. The median total direct costs were higher in confirmed compared to presumptive patients (USD 27.4 [IQR 18.7-48.4] *vs*. USD 19.8 [IQR 13.8-34.0], p=0.02), as were the indirect costs (USD 66.9 [IQR 35.5-150.0] *vs.* USD 46.8 [IQR 20.1-115.3], $p<0.001$). The indirect costs were higher in men compared to women (USD 64.6 [IQR 31.8-159.1] vs. USD 55.6 [IQR 25.1-141.1], p<0.001). The median total distance from patients' household to healthcare facilities for confirmed and presumptive TB patients was 2,338 meters (IQR 1,373-4,122) and 2,009 meters (IQR 986-2,976) respectively.

Conclusions: Confirmed TB patients have complex pathways and higher costs of care compared to presumptive TB patients, but their costs are also substantial. Improved access to healthcare is needed for effective patient-centred care. This

underscores the need for strengthening the healthcare sector and identifying strategies for diagnostic procedures that are cost-effective and patient-centred, particularly in the light of the introduction of new TB diagnostics

Strengths and limitation of the study

- We present data on pathways to care and assess costs of care in confirmed and presumptive TB patients in Tanzania
- We estimate costs of care by stratifying costs according to poverty status and gender
- Estimated costs for TB diagnosis did not account for HIV and other comorbidities.
- The accuracy of reported costs may have been compromised by recall bias

3.1 Introduction

Confirmed and presumptive tuberculosis (TB) patients follow complex pathways to healthcare. Pathways to healthcare are the steps/ways the confirmed and presumptive patients take from the initial point of seeking healthcare to the point of diagnosis and treatment (Hanson et al., 2017; WHO Stop TB partnership, 2016). Many patients consult various healthcare providers before being diagnosed with TB (Said et al., 2017; Shete P.B et al., 2015). These pathways are usually complex and delayed diagnosis and treatment may increase morbidity and mortality (Kapoor et al., 2012). The World Health Organisation estimated an incidence of 10.4 million TB cases in 2016, yet only 6.3 million new TB cases were notified to national authorities and reported to WHO (WHO, 2017). Although many factors contribute to this notification shortfall, the complexity of pathways to TB care may substantially contribute to low notification rates.

TB is widely regarded as a disease of poverty due to its disproportionate effects on the marginalized populations (Ali, 2014; Lönnroth et al., 2009). To help socially and economically marginalized groups fight the disease, healthcare facilities diagnose and treat TB free of charge in countries with a high TB burden (WHO, 2016). However, patients with symptoms of TB face high direct and indirect costs for diagnosis and treatment (de Cuevas et al., 2016; Kemp et al., 2007; Ramma et al., 2015; Tanimura et al., 2014), and these costs are usually higher for patients with confirmed TB than presumptive cases (Shete P.B et al., 2015; Veesa et al., 2018).

Prior to diagnosis, the pathways to care of presumptive TB in Tanzania are complex. They usually involve consultations with more than one healthcare provider with suboptimal or no means for diagnosing TB (Said et al., 2017; Senkoro et al., 2015b). The complex pathways to care may begin at pharmacies and basic health care

facilities with no TB diagnostics before reaching healthcare facilities with TB diagnostic capacity (Veesa et al., 2018).

A national TB prevalence survey indicated that the case detection rate of TB was below 50% (Ministry of health and Social welfare, 2013). This result may not only be due to the complexity but also the high cost of care (Mfinanga and Mutayoba, 2008a; Senkoro et al., 2015b; Eliud R. Wandwalo and Mørkve, 2000a). The recommended pathway to care for TB patients is to present themselves to the appropriate healthcare facilities for TB diagnosis after recognition of TB symptoms (Ministry of health and social welfare, 2006a; Ngadaya et al., 2008a; WHO, 2016).

Research has focused predominantly on patients who have already been diagnosed within the healthcare system, rather than costs for presumptive TB cases prior to diagnosis (Onazi et al., 2015). Costs for presumptive cases are not well understood, especially in sub-Saharan Africa (Alobu et al., 2013; Shete P.B et al., 2015). In addition to financial costs, sociocultural and gender-related factors can shape how patients seek healthcare (WHO, 2005c), yet such studies of the influence of these factors are scarce (Somma et al., 2008a). Finally, only few studies have examined pathways and costs of seeking health care by comparing confirmed and presumptive TB patients (de Cuevas et al., 2016; Laokri et al., 2014; Shete P.B et al., 2015).

Objective

We aimed to assess the pathways to care and associated costs of seeking care from the onset of symptoms until TB diagnosis in confirmed and presumptive TB patients in Dar es Salaam, Tanzania.

3.2 Methods

Study setting and study population

The study was conducted within the framework of an on-going TB cohort study among the adult population in the Temeke district of Dar es Salaam, Tanzania (Said et al., 2017). The district is densely populated with a population of 1,369,000 persons (The United Republic of Tanzania, 2013a). It ranks as the poorest in the region with 29% of the households living below the poverty line, resulting in 295 poor persons per square kilometre (The United Republic of Tanzania, 2005). The number of health facilities in Temeke district is low compared to other districts in the region. There are six public or private hospitals, eight health centers, and 121 dispensaries (The United Republic of Tanzania, 2014a). In 2011, a total of 4,112 TB cases of all forms were notified in the Temeke district, of which 1,760 (43%) were smear-positive (Ministry of Health and Social Welfare, 2014a).

We included adult, sputum smear-positive TB patients and presumptive TB cases who were consecutively enrolled in the TB-DAR study (Mhimbira et al., 2017; Said et al., 2017) between August 2016 and January 2017, until the target sample size of 100 patients in each category was reached (Figure 6). Based on power calculation and previous studies (Laokri et al., 2014; Shete P.B et al., 2015) we included 100 confirmed TB patients and 100 presumptive TB patients allowing to detect a statistically significant difference in the prevalence of diagnostic delay between the two groups of patients with a power of 80% in case of a true difference of at least 20%. Inclusion criteria were, (i) ≥18 years of age at recruitment; (ii) bacteriologically confirmed TB diagnosis, or with presumptive TB, and (iii) residency in the Wailes I or II sub-districts of Temeke. Additionally, patients in both groups were screened for TB

using sputum smear microscopy and Xpert MTB/RIF. We excluded patients who did not provide consent and those with incomplete data.

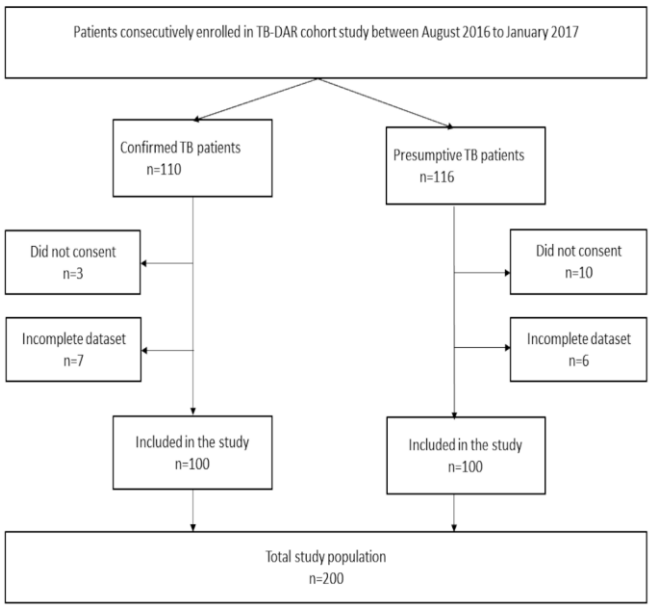

Figure 7.Flowchart of the study population

Data collection

Interviews

We interviewed patients, reconstructed retrospectively visits to healthcare facilities and collected data on direct and indirect costs using a standardized questionnaire at the TB clinic. The data collected included patient socio-demographic and socioeconomic characteristics, TB symptoms, the duration of the time from the onset of symptoms until the first help seeking in a healthcare facility, and the number of health care facilities that confirmed and presumptive TB patients had visited. Data were recorded on tablets using the OpenDataKit (ODK) application (Steiner et al., 2016).

Pathways to care

Visualization charts were used to reconstruct the pathways to care for each patient from the onset of symptoms until TB diagnosis up to five visits. We assessed all visits to the healthcare facilities made, including transport used and approximate distance from the household to the respective healthcare facilities. Healthcare facilities included pharmacies, dispensaries, health centres, traditional and religious healers, and private and government hospitals.

Geographical information system data

We collected geo-coordinates of health care facilities, including all pharmacies, dispensaries, private and governmental hospitals, health centres as well as traditional healers identified in the study area. We also collected geo-coordinates of households of all patients who participated in the study.

Costs of care

We asked patients to estimate direct and indirect costs associated with each visit from the onset of symptoms until TB diagnosis, using a standardized questionnaire (WHO, 2008). Direct costs included costs for diagnosis (such as costs for X-rays), medical costs (as costs for drugs that excluded TB drugs), food, transport, and other costs that included special supplements and vitamins. Indirect costs included income reduction, decreased

production costs, coping costs (including the use of savings or selling of household assets to cater for sickness), and reduced payment for labour. Calculation of patient costs relied upon the 2008 WHO tool (WHO, 2008). We report costs as US Dollars (USD), converted from Tanzania shillings using the exchange rate from the Bank of Tanzania of USD/TZS 2167.84 as of August 2016.

Definitions

A new TB patient was defined by bacteriological confirmation with sputum smear microscopy and/or Xpert MTB/RIF in the absence of prior TB treatment during screening (WHO, 2013). A presumptive TB patient was defined by presentation with TB symptoms, including coughing for longer than two weeks, fever, night sweats, or unexplained weight loss, and who tested negative on sputum smear or Xpert MTB/RIF (WHO, 2013). Diagnostic delay was defined according to the framework of WHO (29) and used in previous studies (Sreeramareddy CT, Oin ZZ, Satyanarayana S, Subbaraman R, 2014; Storla et al., 2008) as the interval between the onset of any TB-related symptom and the time of TB diagnosis of more than 3 weeks. Healthcare provider was defined as a person or facility that could provide healthcare, this included hospitals, pharmacies, and dispensaries, as well as traditional healers. Prior medication was defined as the use of any prescribed or self-prescribed medication prior to TB diagnosis (Said et al., 2017). We defined patients as poor if their wealth fell in the lowest or second-lowest wealth quintile. The non-poor were defined as persons in the remaining middle, fourth, and highest wealth quintiles (Ministry of Health and Social Welfare, 2016b).

Statistical and geographical analysis

We performed descriptive analyses to summarize the data and used χ^2 or Fisher`s test to assess differences between groups in categorical variables. “A cut off point of 300 USD was used as a threshold for the monthly household income as indicated in another similar study (Said et al., 2017). Cost distributions were described by their medians and interquartile ranges (IQR). Costs were further calculated stratifying by gender and poverty status. Wealth quintiles were generated following a principal component analysis of standard household assets as indicated in the Tanzania

household survey (The United Republic of Tanzania, 2013a). To stratify among the poor and non-poor, we used wealth indicators relating to household characteristics (e.g., roofing type, cooking fuel and nature of flooring) and ownership of assets (e.g., radio and mobile phone) to create wealth ranking as used in other studies (Kuwawenaruwa et al., 2015; Vyas and Kumaranayake, 2006). Patients in the first and second quintiles were considered poor and in the remaining quintiles as non-poor. We used the nonparametric Kruskal-Wallis test to assess the statistical significance of the differences in estimated costs between groups. All significance tests were two-sided with a confidence level of 95%. Quintile regression models were performed for median costs to examine the association of patient factors with the different types of costs. Factors considered in these models included male *vs* female, age in years, unskilled and semi-skilled labour, level of education, and diagnostic delay. Statistical analyses were performed using Stata version 14.0 (Stata Corporation, College Station, TX, USA).

We mapped and visualized the pathways of patients to health care providers up to a maximum of five visits for the current episode of sickness as described elsewhere (Shete P.B et al., 2015; Veesa et al., 2018). We calculated distances in meters as the straight-line distance between the patient's household and the nearest health facility. The resulting distances were imported into Stata for further analyses. All geographical analyses were performed using ArcGIS (version 10.5, Esri, Redlands, CA, USA).

Ethics approval and consent to participate

The study was approved by Ifakara Health Institute Institutional Review Board (IHI/reference no IHI/IRB /09-2016), the Medical Research Coordinating Committee of the National Institute for Medical Research in Tanzania (NIMR reference no

NIMR/HQ/R.8c/Vol. I/357), and the Ethics Committee of the Canton of Basel (EKNZ reference no BASEC UBE-2016-00260). Written informed consent was obtained from all study participants.

3.3 Results

Patient characteristics

The study population includes 100 confirmed and 100 presumptive TB patients (Table 1). Patients' median age was 34 years, with presumptive TB patients being slightly older than the confirmed patients. Men slightly predominated (55.5%) and accounted for almost two thirds of the confirmed patients. Compared to presumptive TB patients, confirmed patients had a somewhat higher education, were less likely to own a house and use a car transport for their first point of care. They more frequently used medication after the onset of symptoms and prior to seeking care at the health facilities (71% *vs.* 44%, p<0.001). The proportion of patients with a monthly household income of less than USD 300 was 63% in confirmed and 75% in presumptive patients (p=0.06).

First point of care and diagnostic delay

Among confirmed patients, 44% first sought care at pharmacies after the onset of symptoms, whereas 42% of presumptive patients first sought care at hospitals (Table 1). Fewer than 10% of patients in both groups reported visits to traditional healers as the first point of care. Confirmed patients frequently indicated more than 2 visits at health facilities (33% *vs.* 9%, p<0.001).

The average time for first seeking healthcare after the onset of symptoms was two weeks. Overall, 45.5% sought care within one week after the onset of TB symptoms. For 30%, the diagnostic was established within 2-3 weeks. For around every tenth there was a diagnostic delay of six weeks or more. The diagnostic delay differed significantly between confirmed and presumptive patients, with 41% of confirmed

versus 50% of presumptive patients having a short delay (of <1 week). Higher proportion of confirmed patients had a diagnostic delay of 4-5 and of ≥6 week

Table 1. Socio-demographic characteristics and diagnostic delay for the confirmed and presumptive tuberculosis (TB) patients

Variable n (%)	All n=200	Confirmed n=100	Presumptive n=100	P-value
Age in years (median, IQR)	34 (27-41.5)	32.5 (26-39)	34 (29-43)	0.055*
Age groups				0.22
18-27 years	52 (26)	30 (30)	22 (22)	
28-37 years	75 (37.5)	39 (39)	36 (36)	
>38 years	73 (36.5)	31 (31)	42 (42)	
Sex				0.016
Male	111 (55.5)	64 (64)	47 (47)	
Female	89 (44.5)	36 (36)	53 (53)	
Education				0.023
No education	34 (17)	12 (12)	22 (22)	
Primary education	122 (61)	59 (59)	63 (63)	
Secondary/university	44 (22)	29 (29)	15 (15)	
Occupation				0.081
Unemployed/housewife	59 (29.5)	30 (30)	29 (29)	
Unskilled labour	49 (24.5)	18 (18)	31 (31)	
Semiskilled labour	92 (46)	52 (52)	40 (40)	
Household size				
<4	93 (46.5)	45 (45)	48 (48)	0.67
≥4	107 (53.5)	55 (55)	52 (52)	
House ownership				0.050
Rented	135 (67.5)	74 (74)	61 (61)	
Own	65 (32.5)	26 (26)	39 (39)	
Household income				0.067
≤300 USD per month	138 (69.0)	63 (63)	75 (75)	
>300 USD per month	62 (31.0)	37 (37)	25 (25)	
Wealth quintile				
Poor -households	47 (23.5)	21 (21)	26 (26)	0.54
Second	33 (16.5)	16 (16)	17.0 (17)	
Middle	41 (20.5)	19 (19)	22 (22)	
Fourth	44 (22.0)	27 (27)	17 (17)	
Non-poor households	35 (17.5)	17 (17)	18 (18)	
Prior Medication				<0.001
Yes	115 (57.5)	71 (71)	44 (44)	
No	85 (42.5)	29 (29)	56 (56)	
First point of care				0.004
Hospitals	70 (35.0)	28 (28)	42 (42)	
Dispensaries	49 (24.5)	19 (19)	30 (30)	
Pharmacies	66 (33.0)	44 (44)	22 (22)	
Traditional healers	15 (7.5)	9 (9)	6 (6)	
HC facility visits				<0.001
≤2	158 (79.0)	67 (67)	91 (91)	
>2	42 (21.0)	33 (33)	9 (9)	
Transport used for first point of care				
Car	70 (35.5)	22 (22)	48 (48)	<0.001
On foot	95 (47.5)	65 (65)	30 (30)	
Motorcycle/tricycle	35 (17.5)	13 (13)	22 (22)	
Diagnostic delay (weeks)				
0-1	91 (45.5	41 (41)	50 (50)	0.04
2-3	60 (30)	26 (26)	34 (34)	
4-5	27 (13.5)	19 (19)	8 (8)	
6+	22 (11)	14 (14)	8 (8)	

HC, health facility; IQR, interquartile range; USD, United States Dollar * Wilcoxon-rank sum test

P-values provided by Chi-square tests and Fisher's exact test

Pathways to care

The spatial distribution of healthcare facilities in the study area show pharmacies and dispensaries are distributed over the whole area Figure 8A. Hospitals are situated mainly in the urban centres and traditional healers predominantly in the peripheral area. Figures (8B) and (8C) offer examples of pathways to care until TB diagnosis in confirmed and presumptive patients. Pathways in confirmed patients involved several visits to the healthcare facilities before TB diagnosis. Pathways in presumptive patients were more direct with only one or few visits to healthcare facilities before TB diagnosis.

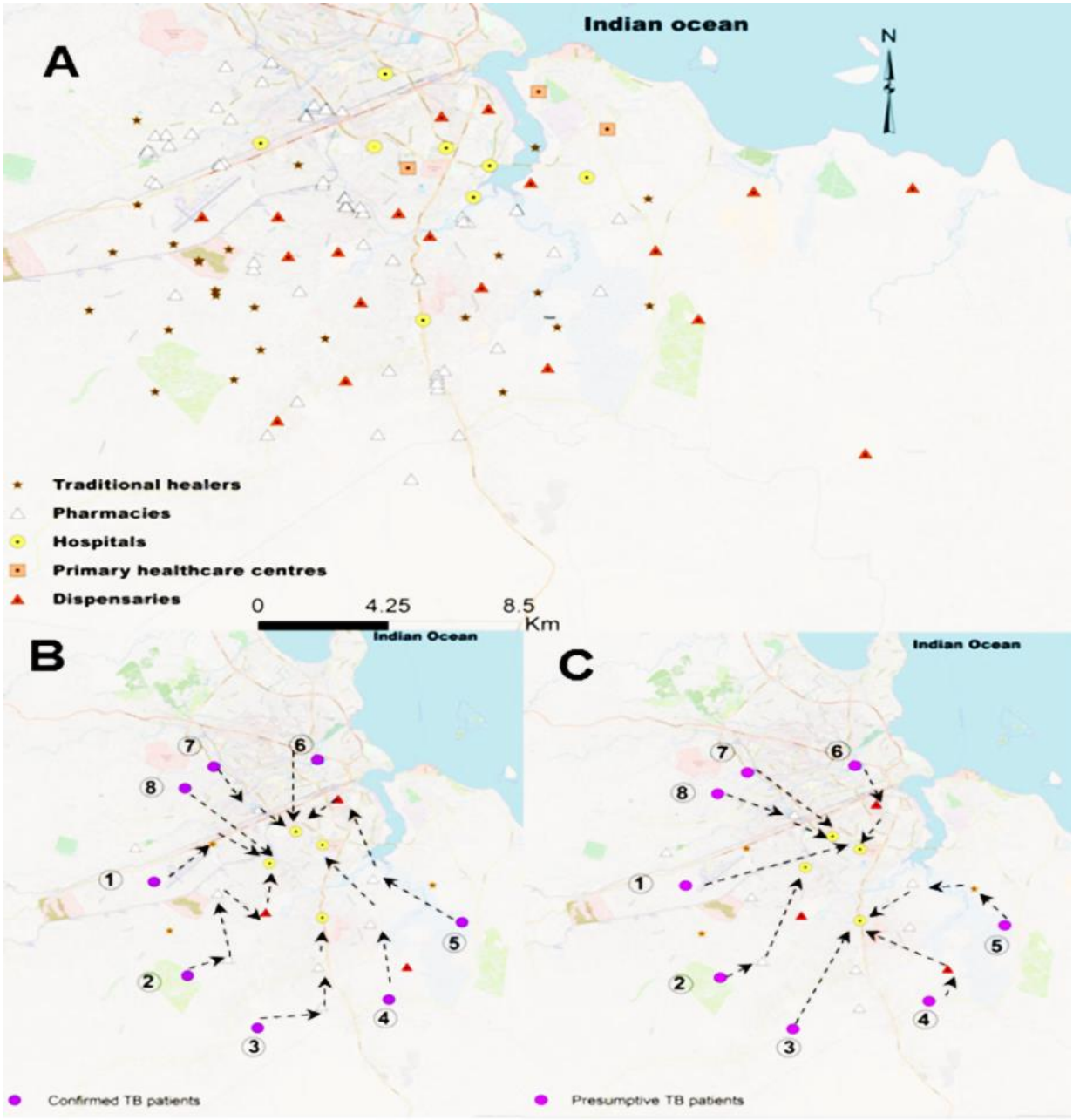

Figure 8. Geographical analyses of health care facilities and pathways to care of confirmed and presumptive TB patients in Temeke District Dar es Salaam Tanzania. **Panel A**: Spatial distribution of healthcare facilities in the study area. **Panel B:** Possible pathways to care of confirmed TB patients while seeking healthcare. Various types of healthcare facilities as the entry point into the healthcare system until final diagnosis at the TB clinic are shown. **Panel C**: Possible pathways to care of presumptive TB patients while seeking healthcare. Various types of healthcare facilities as the entry point into the healthcare system until final diagnosis at the TB clinic are shown.

The median total distance from patients' households to healthcare facilities including hospitals, pharmacies, dispensaries, and traditional healers was 2,338 meters (IQR 1,373-4,122) for confirmed patients, and 2,009 meters (IQR 986-2,976) for presumptive patients (p=0.25). Among confirmed patients, 37% lived within 500 meters near a pharmacy, as did 42% of presumptive patients. Eighty-three per cent of confirmed patients and 72% of presumptive patients lived within 1,000 meters from the nearest hospital. We did not find an association of the distance from patients' household to the nearest possible healthcare facility with patient characteristics such as being poor (defined as being in the lowest wealth quintile), prior use of medication, or having more than two healthcare visits in multivariate analysis.

While seeking care at pharmacies was prominent for the first visit in confirmed patients and also reported by a fifth of the presumptive patients, subsequent visits at pharmacies were mentioned much less (Figure 9). The second visit was characterised by a large proportion of both patients seeking healthcare at hospitals. Confirmed patients had more visits to healthcare facilities compared to presumptive patients (none of the presumptive patient's indicated a fourth and fifth visit).

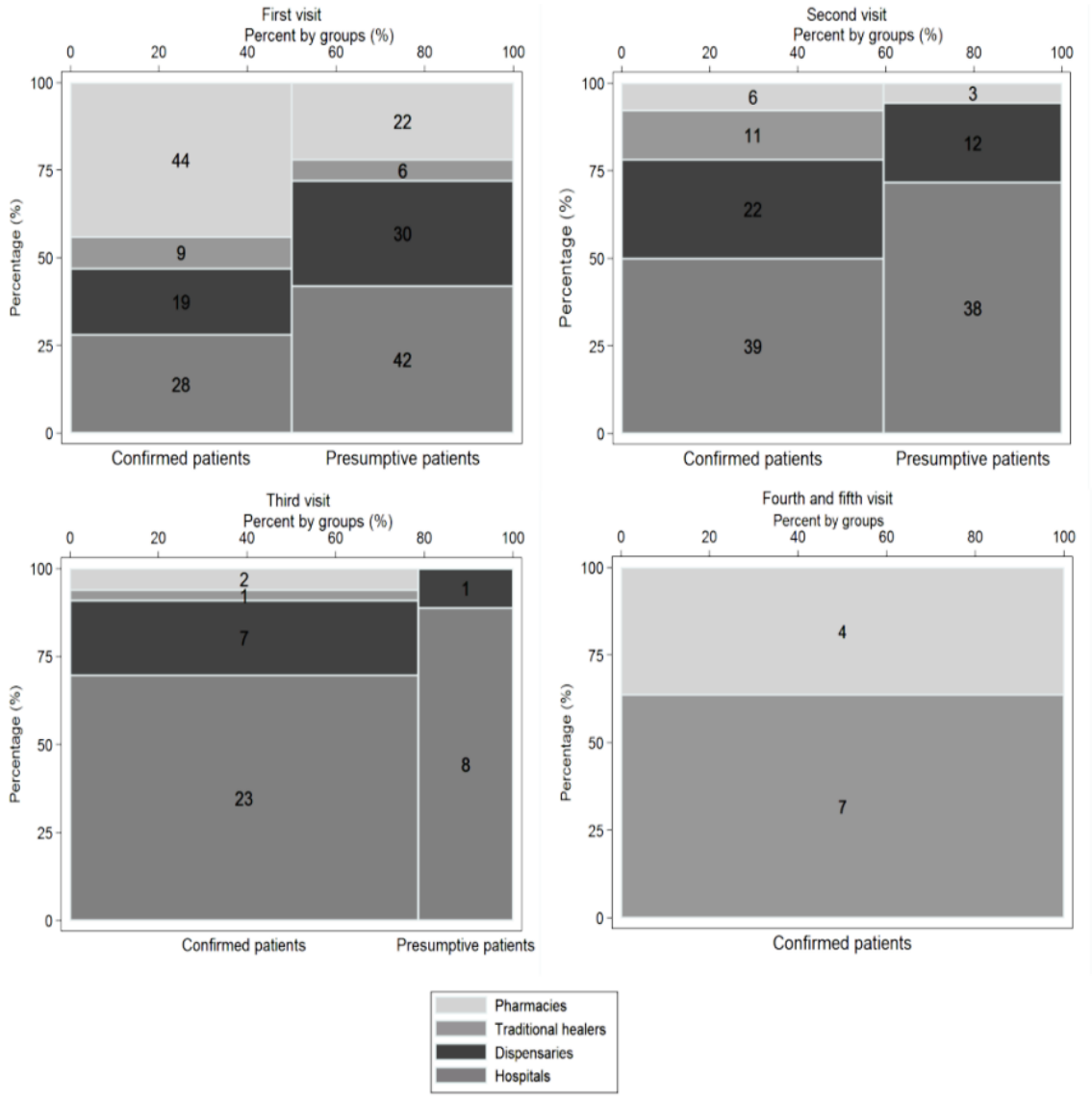

Figure 9. Margin plots showing associations between total costs and diagnostic delay in confirmed TB patients (panel A) and presumptive TB patients (panel B). Associations between median total costs and diagnostic delay were modelled by quadratic polynomials. The p-values are from Wald test of the linear and quadratic terms of the diagnostic delay (p<0.001 for panel A, p=0.08 for panel B)

Costs associated with seeking care

Patients spent a median of 31% (IQR 15.0-56.3%) of their monthly household income for health expenditures for all visits for TB diagnosis. For the first visit confirmed patients had lower median costs than presumptive patients (USD 8.3 [IQR 4.6-17.5] *vs.* 13.8 [IQR 6.0-20.5]), but their costs were comparatively higher with increasing number of visits (Supplementary Table 1).

Overall, indirect costs were considerably higher than direct costs, both in confirmed and presumptive patients from the onset of symptoms until confirmation/exclusion of TB (Table 2). Confirmed patients had higher diagnostic costs than presumptive patients (USD 7.0 [IQR 5.8-9.2] and 5.3 [IQR 1.4-7.0), higher food costs, and higher informal payments. Among the indirect costs, income reduction was considerably higher for confirmed TB patients than presumptive patients. (USD 23.1 [IQR 6.9-55.4] *vs.* 9.2 [IQR 1.4-25.4]).

Table 2. Direct and indirect costs (in USD) from the onset of symptoms until confirmation/exclusion of TB among confirmed and presumptive TB patients.

Costs	All (n=200)	Confirmed TB patients (n=100)	Presumptive TB patients (n=100)	P-value
Average number of visits (range)	1.2 (1-5)	1.3 (1-5)	1.1 (1-3)	
Direct costs	Median, (IQR)	Median, (IQR)	Median, (IQR)	
Diagnostic costs	7.0 (2.3-8.8)	7.0 (5.8-9.2)	5.3 (1.4-7.0)	<0.001
Medication costs	2.8 (1.4-8.0)	2.8 (1.4-9.2)	2.8 (1.4-7.4)	0.873
Food costs	2.3 (1.4-4.2)	3.2 (1.8-5.3)	1.8 (1.0-2.5)	<0.001
Transport costs	3.2 (1.8-5.5)	3.2 (1.4-5.5)	3.7 (1.8-6.00)	0.154
Informal payments	2.3 (1.4-4.2)	2.8 (2.3-7.4)	2.1 (1.0-2.8)	<0.001
Other direct costs	4.6 (2.3-9.7)	4.6 (2.3-9.5)	4.4 (2.3-9.7)	0.567
Sub-total direct costs	24.7 (16.1-42.4)	27.4 (18.7-48.4)	19.8 (13.8-33.9)	0.02
Indirect costs (median, (IQR)				
Coping costs	11.3 (4.6-23.1)	11.5 (4.61-20.98)	9.2 (4.6-27.7)	0.765
Income reduction	15.7 (3.7-36.9)	23.1 (6.9-55.4)	9.2 (1.4-25.4)	0.001
Decreased production	9.2 (1.4-23.06)	10.0 (3.2-26.3)	9.2 (0-16.8)	0.137
Less paid labour	4.61 (0-12.0)	5.07 (0-15.22)	4.61 (0-9.2)	0.467
Other indirect costs	8.5 (1.8-19.4)	11.8 (1.4-23.1)	6.5 (2.3-13.8)	0.056
Sub-total indirect costs	60.0 (25.1-141.1)	66.9 (35.1-149.9)	46.8 (20.1-115.3)	0.006
Total costs	83.0 (46.4-173.9)	99.2 (64.3-190.0)	67.11 (37.1-161.0)	0.003

IQR, interquartile range; TB, tuberculosis; USD United States Dollar (1 USD=2168 Tanzania shillings, exchange rates as of August 2016). P-values provided by Wilcoxon rank sum test.

Gender, poverty status and costs

Costs for different patients groups differed significantly. Overall, the median total direct costs were similar for men, USD 24.9 (IQR 17.5-41.9), and women, USD 24.6 (IQR 16.1-42.4 p=0.66). Indirect costs for men, USD 64.6 (IQR 31.8-159.1), were significantly higher than those for women, at USD 55.6 (IQR 25.1-141.1, p<0.001). Analyses stratified by sex and poverty status indicate that poor men with confirmed TB had lower total direct costs compared to poor women (USD 24.4 [IQR 18.9-47.9] *vs.* 30.0 [IQR 18.68.5-49.58.]) (Table 3). For the presumptive TB patients total direct costs for poor men differed slightly from those of poor women (USD 22.6 [IQR 17.5-29.1] *vs.* 20.5 [IQR 14.3-35.1]). Among the non-poor men and women, direct costs varied only little in confirmed and presumptive patients. In confirmed patients, diagnostic costs were lower among poor men compared to poor women (USD 6.91 [IQR 4.61-9.22] *vs.* 7.61 [IQR 1.38-10.14]), whereas for the presumptive patients, diagnostic costs were the same among poor men and women

Table 3. Direct costs (in USD) of seeking healthcare among confirmed and presumptive TB patients, according sex and poverty status

Variable	All	Confirmed				Presumptive			
		Men		Women		Men		Women	
Median (IQR)		Poor[1] n=21	Non-poor[2] n=43	Poor n=16	Non-poor n=20	Poor n=15	Non-poor n=32	Poor n=28	Non-poor n=25
Diagnostic costs	6.92 (3.22-9.23)	6.91 4.61-9.22	6.91 (6.91-9.22	7.61 (1.38-10.14)	7.61 1.84-11.53	4.61 (0.92-6.91)	6.91 (2.07-9.68)	4.61 (1.84-6.91)	6.91 (3.22-9.22)
Medication costs	3.69 (1.84 -8.99)	5.53 (2.30-16.14)	2.30 (1.38-6.91)	3.45 (0.92-8.76)	3.92 (2.07-13.60)	4.15 (1.38-9.22)	5.30 (2.30-8.76)	3.45 (1.84-8.99)	3.69 (2.30-6.91)
Food costs	2.31 (1.38-4.61)	3.22 (1.84-6.45)	4.15 (1.84-5.07)	2.53 (1.84-6.68)	3.45 (2.30-6.22)	1.38 (0.92-2.30)	2.07 (1.15-2.99)	1.84 (0.92-2.53)	2.30 (0.92-2.76)
Transport costs	3.69 (1.84-5.76)	3.69 (1.84-5.53)	2.76 (1.38-5.53)	3.00 (0.69-4.84)	3.69 (2.07-5.53)	3.22 (1.38-5.07)	4.38 (2.53-6.91)	3.69 (2.07-6.45)	4.61 (2.30-6.00)
Informal payments	2.30 (1.38-4.61)	2.30 (2.30-6.45)	2.30 (2.30-9.68)	3.22 (2.30-12.91)	3.92 (1.61-7.38)	1.84 (0.92-2.30)	2.30 (1.61-3.69)	1.16 (0.92-3.22)	2.30 (0.92-2.77)
Other direct costs	5.53 (2.77-10.61)	5.07 (2.30-6.45)	6.45 (3.69-10.60)	6.91 (4.84-8.30)	9.91 (4.84-15.00)	5.07 (1.38-9.68)	5.30 (2.07-12.00)	3.45 (2.30-10.60)	5.53 (3.69-10.60)
Total direct costs	27.21 (18.45-43.12)	24.44 (18.91-47.97)	29.98 (22.60-43.35)	30.00 (18.68-49.58)	32.51 (17.98-55.81)	22.60 (17.52-29.05)	25.13 (15.91-44.28)	20.52 (14.29-35.05)	26.75 (17.98-37.82)

IQR, interquartile range; USD, United States Dollar (1 USD=2168 Tanzania shillings, exchange rates as of August 2016) Other direct costs including costs of special supplements and vitamins required due to illness or additional direct costs due to chronic illness for which patients were receiving treatment for besides the costs for TB diagnosis.

[1] Poor or second lowest wealth quintile

[2] Non-poor middle, fourth and highest wealth quintile.

Total indirect costs, (Table 4) among poor confirmed TB patients were higher in men than women, (USD 84.4 [IQR 55.3-125] *vs.* 51.7 [IQR 27.6-73.4]), while this gender difference was absent in non-poor confirmed patients. Among presumptive TB patients, poor men faced higher total indirect costs than poor women (USD 50.2 [IQR 27.6-83.4]) *vs.* 39.2 [IQR 18.6-116.0]).

Table 4 Indirect costs (in USD) of seeking health care among confirmed and presumptive TB patients, according to sex and poverty status

Variable	All	Confirmed				Presumptive			
		Men		Women		Men		Women	
Median (IQR)		Poor n=21	Non-poor n=43	Poor n=16	Non-poor n=20	Poor n=15	Non-poor n=32	Poor n=28	Non-poor n=25
Coping costs	13.37 (6.91-25.36)	10.60 (4.61-18.45)	13.83 (6.91-20.75)	13.53 (8.53-17-75)	23.06 (9.22-34.59)	9.22 (6.91-13.83)	13.37 (4.61-27.67)	15.91 (6.22-140-35)	9.22 (0-18.45)
Income reduction	18.45 (4.61-35.51)	29.98 (23.06-46.12)	23.06 (11.53-59.96)	14.52 (5.76-28.13)	23.06 (0-53.04)	9.22 (3.69-36.90)	15.22 (6.68-29.98)	4.61 (0.69-11.53)	11.53 (0-23.06)
Decreased production	9.22 (2.30-23.06)	16.14 (7.38-23.06)	12.00 (4.61-31.36)	6.91 (2.30-13.37)	9.45 (0-32.51)	9.22 (4.61-20.75)	13.14 (4.61-31.13)	4.61 (0-13.14)	9.22 (0-14.76)
Less paid labour	4.61 (0-12.0)	6.91 (0-17.52)	6.91 (0-18.45)	0 (0-6.45)	1.61 (0-18.45)	5.53 (0-13.83)	5.75 (0-13.37)	4.61 (0-10.37)	1.38 (0-6.91)
Other indirect costs	8.53 (1.38-19.37)	11.53 (1.38-26.29)	12.0 (0-23.06)	11.53 (2.53-18.45)	11.53 (3.69-26.06)	9.68 (3.22-13.83)	8.53 (4.38-21.90)	5.76 (0.69-11.07)	3.22 (0.92-9.22)
Total indirect costs	61.34 (27.90-128)	84.40 (55.35-125)	71.03 (51.66156.36)	51.66 (27.67-73.80)	70.80 (31.82-148.52)	50.27 (27.67-83.48)	55.11 (30.21-166.28)	39.20 (18.68-116.00)	39.20 (21.67-65.95)

IQR, interquartile range; USD, United States Dollar (1 USD=2168 Tanzania shillings, exchange rates as of August 2016)

Other indirect costs including costs that were not treated as direct labour or additional indirect costs due to chronic illness for which patients were receiving treatment for besides the costs for TB diagnosis

[1] Poor or second lowest wealth quintile

[2] Non-poor middle, fourth and highest wealth quintile

Determinants of cost differences

On average, each week of diagnostic delay was associated with an increase in median total costs (direct and indirect costs) among confirmed patients by 1.44 USD (95%CI: (-19.56, -6.63), p <0.001), but no significant association was seen in presumptive patients (Table 5). Diagnostic delay was associated with an increase in total direct costs in confirmed patients (USD 0.52 per week, 95%CI: (0.34, 0.70), p<0.001), but with a decrease in presumptive patients (USD -0.84 per week, 95%CI: (-1.32,-0.35), p=0.001). For total indirect costs, the pattern was similar, but neither of the two associations reached statistical significance.

Table 5. Estimates of effects of different factors on median direct, indirect and total costs in USD among confirmed and presumptive TB patients

Variable	All			Confirmed			Presumptive		
	*Difference	95% CI	P-value	*Difference	95% CI	P-value	*Difference	95% CI	P-value
Total direct costs									
Males vs females	-1.71	-11.80, 8.38	0.73	-2.31	-20.29, 15.67	0.79	-3.58	-9.80-2.63	0.25
Age (per year)	-0.01	-0.48, 0.46	0.97	0.28	-0.70, 1.26	0.57	0.06	-0.19, 0.31	0.31
Unskilled labour[1]	1.80	-11.40, 15.01	0.78	-7.55	-33.38, 18.26	0.56	2.20	-5.18, 9.59	0.55
Semi-skilled labour[1]	2.87-	-8.75, 14.48	0.62	5.01	-14.66, 24.69	0.61	1.87	-5.49, 9.23	0.61
Poor vs non-poor	-2.34	-12.19, 7.51	0.63	19.73	--56.98, 96.46	0.61	-2.40	-8.07, 3.27	0.40
Primary education[2]	3.18	-10.21, 16.56	0.64	8.96	-17.83, 35.76	0.66	0.66	-6.47 7.78	0.85
Secondary education	6.12	-11.16, 23.40	0.48	20.86	-11.40, 53.12	0.20	4.22	-5.88, 14.32	0.40
University[2]	9.36	-19.07, 37.84	0.51	10.53	-35.17, 56.25	0.46	-0.59	-21.14, 19.95	0.95
Diagnostic delay	0.04	-0.08,0.16	0.52	0.52	0.34, 0.70	<0.001	-0.84	-1.32,-0.35	0.001
Total indirect costs									
Males vs females	11.63	-11.37, 34.63	0.32	6.60	-33.93, 47.14	0.74	1.85	-34.74, 38.44	0.92
Age (per year)	0.38	-0.69-1.45	0.48	0.07	-2.14, 2.29	0.94	0.75	-0.74, 2.24	0.32
Unskilled labour	12.68	-17.41, 42.78	0.40	14.47	-43.74, 72.700	0.62	19.13	-24.32, 62.11	0.38
Semi-skilled labour	20.90	-5.58, 47.38	0.12	37.24	-7.11, 81.60	0.09	22.94	-20.38, 66.27	0.29
Poor vs non-poor	6.29	-16.15, 28.75	0.58	6.92	-33.36, 47.20	0.73	5.82	-27.53, 39.18	0.72
Primary education	21.24	-9.27, 51.75	0.17	8.96	-51.46, 69.37	0.76	20.0	-20.34, 60.34	0.32
Secondary/ University	70.14	9.47, 130.80	0.02	56.88	11.71, 125.47	0.10	-38.5	16.52, 93.52	0.16
Diagnostic delay	0.46	0.18-0.74	0.001	0.57	0.16, 0.97	0.07	-1.25	-4.11, 1.60	0.38
Total costs									
Males vs females	9.87	-26.39, 46.14	0.59	-4.98	-58.90, 48.93	0.85	-0.62	-44.96, 43.71	0.97
Age (per year)	0.34	-1.34, 2.03	0.68	-0.56	-3.50, 2.38	0.70	0.74	-1.06, 2.55	0.41
Unskilled labour	11.95	-35.50, 59.40	0.62	8.25	-69.18, 85.69	0.83	16.02	36.64, 68.69	0.54
Semi-skilled labour	30.47	-11.28, 72.23	0.15	58.81	-0.18, 117.81	0.05	26.64	-25.86, 79.14	0.31
Poor vs non-poor	0.89	-34.50, 36.31	0.96	8.39	-45.18, 61.98	0.75	2.39	-38.01, 42.81	0.90
Primary education	24.87	-23.25, 72.98	0.31	19.73	-60.62, 100.09	0.62	18.06	-32.75, 68.88	0.48
Secondary education	69.54	7.43, 131.16	0.02	69.45	-27.29, 166.19	0.15	46.10	-25.86, 79.14	0.20
University	108.89	6.63, 211.16	0.03	69.20	-67.87, 206.28	0.31	-15.74	-162.23, 130.73	0.83
Diagnostic delay	1.29	0.84.1.73	<0.001	1.44	-19.56, -6.63	<0.001	-2.40	-5.86,1.06	0.17

*Estimated differences in median costs are presented with the corresponding 95% confidence intervals (95% CI); Diagnostic delay was defined as delay in seeking care three weeks or more after the onset of symptoms. Multivariable quintile regression was performed for median costs to examine the association of patient factors with different types of costs. Separate models were run for direct, indirect and total costs.

[1] Reference: Unemployed

[2] Reference: no educatio

Overall, having a university degree was significantly associated with higher indirect costs (USD 70.14, 95%CI: (9.47, 130.80), p=0.02). None of other factors of the model were significantly associated with median costs. The pattern of positive association between diagnostic delay and total costs among confirmed patients and negative association among presumptive patients was further supported by analyses using linear and quadratic terms (Figure 10).

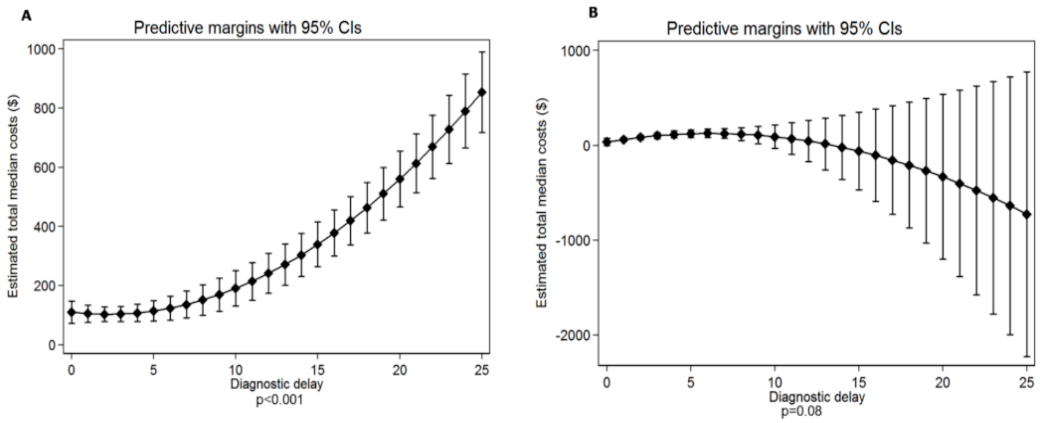

Figure 10. Margin plots showing associations between total costs and diagnostic delay in confirmed TB patients (panel A) and presumptive TB patients (panel B). Associations between median total costs and diagnostic delay were modelled by quadratic polynomials. The p-values are from Wald test of the linear and quadratic terms of the diagnostic delay (p<0.001 for panel A, p=0.08 for panel B)

Furthermore, we conducted regression analyses separately for different types of costs (Supplementary table 2 and Supplementary table 3). Medication costs in confirmed patients increased with the number of weeks of delay (USD 0.13 per week, 95%CI: (0.06, 0.19), p<0.001), but not in presumptive patients. Transport costs were significantly lower among men and women with presumptive TB (USD -1.54, 95%CI: (-3.12, -0.03), p < 0.05). We further observed an increase in coping costs with the length of diagnostic delay in both confirmed and presumptive patients (Supplementary Table 3). Finally, in patients with presumptive TB, costs due to

decreased production were significantly higher among unskilled labourers (USD 8.71, 95%CI: (0.53, 16.89), p=0.03).

3.3 Discussion

This study indicates that pathways to care of the confirmed TB patients are more complex compared to those of presumptive patients, involving visits at several healthcare providers among whom not all have necessary diagnostic equipment. A diagnostic delay of six weeks or more after the onset of symptoms was reported by 10% of the patients. Fifty percent of the patients visited healthcare facilities within one week after onset of symptoms. In seeking care, patients incur substantial direct and indirect costs. The costs of care were higher in confirmed patients than in presumptive patients. For half of the confirmed patients, direct costs account for more than 30% of the monthly household income. Total costs were associated with diagnostic delay among confirmed patients only. The indirect costs were higher for men than for women whereas direct costs did not differ. Among the poor, direct costs were higher in women and indirect costs higher in men.

Almost half of the confirmed TB patients began their search for care at pharmacies, and patients in both groups sought care from more than one healthcare provider before a diagnosis. This highlights a diagnostic shortfall in some healthcare facilities and poor management of patients as documented elsewhere (Laokri, 2017), and partially explains the diagnostic delay. Compared to findings of other studies (Getnet et al., 2017a; Ngadaya et al., 2008a) the observed diagnostic delay in our study was lower. However, a delay of at least 6 weeks observed in 10% of our study population still requires attention. Most patients lived near healthcare facilities, and only 9% of the confirmed TB patients and 6% of the presumptive TB patients reported visiting traditional healers. Living near healthcare facilities might have an impact on treatment seeking (Lake et al., 2011). We investigated the impact of geographical distance between household and health facility on health-seeking behaviour, but

found no associations between distance and patient characteristics such as being poor, prior use of medication and having more than two visits to the healthcare facility. This is contrary to some other results that found distance to have an impact on patient characteristics such as treatment completion and diagnostic delay (Cai et al., 2015; Ibrahim et al., 2014; Sreeramareddy CT, Oin ZZ, Satyanarayana S, Subbaraman R, 2014). Diagnostic delay was significantly associated with direct costs, indirect costs (borderline significance) and total costs in confirmed patients. The most likely explanation for this finding is that diagnostic delay worsens patients' morbidity, especially in confirmed TB patients, thus increasing costs of healthcare (Cai et al., 2015).

Patients in both groups spent a median proportion of around 30% of their monthly household income on health expenditures for up to five visits. The economic burden of direct and particularly indirect costs of seeking TB care for patients and their households are high for the marginalized population, which is most at risk of acquiring TB. These findings are consistent with other studies that show patients in low-and-middle income countries face a very high economic burden of seeking TB care (Tanimura et al., 2014), and expenditures for seeking healthcare for TB can cause or exacerbate poverty (Barter et al., 2012a). The total costs for presumptive TB patients were lower compared to confirmed cases in our study. These results are also consistent with those reported in other settings where half of the total costs for seeking healthcare are pre-treatment costs which disproportionately affect poor TB patients (Tanimura et al., 2014)

While direct costs were relatively low, they may be catastrophic for patients who are semiskilled labourers reporting monthly household income of less than 300 USD. Their situations can further be worsened by employment in the informal sector that

lacks sickness benefits (Barter et al., 2012a). Confirmed TB patients encountered higher indirect costs compared to presumptive patients, which may be due to the prolonged time required for diagnosis leading to their substantially higher income reduction as shown in our study.

We found higher indirect costs among poor men compared to poor women. This was mainly due to their more pronounced income reduction and decreased production. Although the direct and indirect costs were higher for men than for women, the costs of ill health are usually more profound for women and their households than for men. When women get sick the impact of the disease on their children and their families is stronger than when men get sick (Kemp et al., 2007). Furthermore, financial burden may limit access to care for both confirmed and presumptive female TB patients since most of them lack financial autonomy. Moreover, their lower status in households deprioritizes their health.

Article summary

Strengths and limitations of this study

Our study is the first to look at pathways to care and assess costs of care before the start of treatment in confirmed and presumptive TB patients in an urban Tanzania setting. Studies have focused on pathways and costs of care in confirmed TB patients and ignore the effects on presumptive cases. Furthermore, it's the first study to estimate costs by stratifying according to poverty status and gender in sub-Saharan Africa. However, this study has some limitations. First, recall bias is a concern when inquiring about the costs incurred during health-care seeking. This might influence the accuracy of the reported costs and pathways to care. However, we attempted to limit the recall bias by linking questions about costs with memorable events such as the onset of symptoms or first care seeking. Our interviews were also

conducted by well-trained personnel who spent enough time with the respondents so as to obtain answers that were as accurate as possible. Furthermore, we only addressed pathways and costs of care until TB diagnosis to the public healthcare facilities. Therefore, we might have left out costs of care for the patients who had their final diagnosis at the private and faith based healthcare facilities. Finally, we only estimated the costs for TB diagnosis. However, comorbidities may have caused higher costs, but this is equally true for confirmed as well as presumptive TB patients.

3.4.1 Conclusions

This study demonstrates the complexity of pathways until diagnosis in confirmed TB patients. It also highlights the high financial burden for the period between symptom onset and diagnosis for confirmed and presumptive TB patients, and points to different direct and indirect costs among poor men and women. This underscores the need to strengthen the healthcare sector to ensure early diagnosis of TB. Ensuring integration of different healthcare providers including private, public health practitioners and patients themselves could help not only in reducing the complex pathways during healthcare seeking, but also effective health care utilization (Laokri, 2017). Reducing the direct and indirect costs associated with treatment seeking is likely to support confirmed and presumptive TB patients in timely accessing health care for TB diagnosis and treatment. Decreasing or removing user fees and further decentralization of TB care could reduce diagnostic delay and lower expenditures. Additionally, strengthening of health systems policies including protection of patients against the catastrophic direct and indirect costs, as well as ensuring universal access to healthcare must be interpreted into actions for a better TB control (Lienhardt et al., 2012). These interventions are central for reaching the ambitious

WHO targets of zero deaths, disease, and suffering due to TB by 2035 (WHO, 2015b).

Supporting Information

Supplementary Table 1. Direct costs associated with first, second and >2 visits for patients with confirmed and presumptive TB

Visit	All n (%)	Cost of visit/patient in USD Median (IQR)		Costs as a % of MMHI Median (IQR)	
		Confirmed	Presumptive	Confirmed	Presumptive
First visit	200 (100)	8.30 (4.6-17.5)	13.8 (6.0-20.5)	9.1 (3.7-18.3)	15.1 (8.0-34.8)
Second visit	90 (45)	15.2 (11.0-24.0)	14.3 (12.0-22.1)	14.5 (8.7-28.5)	19.7 (10.0-32.0)
Third to fifth visit	42 (21)	27.2 (14.8-38.7)	13.4 (12.9-20.3)	24.6 (13-42)	13.3 (12.0-14.3)
Total direct costs		27.4 (18.7-48.4)	19.8 (13.8-34.0)	30.5 (16.5-53.5	29.0 (14.1-52.1

IOR, interquartile range; USD, United States Dollar (1 USD=2168 Tanzania shillings, exchange rates as of August 2016); MMHI, median monthly household income

Supplementary Table 2. Estimates of effects of different factors on median types of direct costs in USD among confirmed and presumptive TB patients.

Variable	All			Confirmed			Presumptive		
	Difference*	95% CI	P-value	Difference*	95% CI	P-value	Difference*	95% CI	P-value
Diagnostic costs									
Males vs females	0.29	-1.33, 1.93	0.71	-0.17	-2.85, 2.52	0.90	-0.95	-3.45, 1.54	0.45
Age (in years)	0.03	-2.67,0.51	0.18	-0.05	-0.20, 0.01	0.45	0.07	-0.03, 0.17	0.18
Unskilled labour[1]	1.71	-0.42,.84	0.11	1.32	-2.53, 5.19	0.49	1.99	-0.97, 4.96	0.18
Semi-skilled[1]	1.22	-0.65,3.10	0.20	1.77	-1.17, 4.71	0.34	2.66	-0.29, 5.62	0.07
Poor vs non-poor	-1.08	-2.67,0.51	0.18	-0.16	2.83, 2.50	0.90	-1.80	-4.08, 0.48	0.12
Primary education[2]	1.14	-1.03, 3.30	0.30	3.03	-0.98, 7.03	0.13	-0.27	-3.12, 2.59	0.85
Secondary education	2.49	0.29, 5.29	0.08	3.80	-1.02, 8.62	0.12	0.89	-3.17, 4.95	0.85
University[2]	6.16	1.56, 10.76	0.09	3.30	-3.53, 10.14	0.34	3.72	-4.54, 11.97	0.37
Diagnostic delay	-0.02	-0.02, 0.19	0.97	0.01	-0.01, 0.04	0.49	-0.07	-0.03, 0.12	0.45
Medication costs									
Males vs females	-0.31	-3.65, 3.09	0.85	-0.69	-7.40, 6.01	0.83	0.45	-2.23-3.13	0.73
Age (in years)	-0.03	0.18, 0.13	0.74	-0.01	-0.38-, 0.35	0.95	-0.05	-0.16, 0.06	0.36
Unskilled labour	0.13	-4.23, 4.49	0.95	-0.03	-9.67, 9.61	0.99	-0.68	-3.86-2.49	0.67
Semi-skilled labour	-0.03	-3.86, 3.81	0.99	0.92	-6.41, 8.27	0.80	-2.01	-5.17, 1.16	0.21
Poor vs non-poor	0.62	-2.64, 3.87	0.71	0.77	-5.90, 7.43	0.82	0.31	-2.12, 2.75	0.80
Primary education	1.26	-3.16-5.68	0.57	2.04	-7.95, 2.04	0.68	0.88	-2.18, 3.95	0.56
Secondary education	1.54	-4.17, 7.25	0.59	4.28	-7.75, 16.32	0.48	0.58	-3.76, 4.93	0.79
University	0.24	9.16, 9.64	0.95	1.98	-15.08, 19.03	0.81	4.24	-4.60, 13.08	0.34
Diagnostic delay	0.06	0.02, 0.10	0.002	0.13	0.06, 0.19	<0.001	-0.17	-0.38, 0.04	0.11
Transport costs									
Males vs females	-1.02	-2.19, 0.13	0.08	-0.52	-2.25, 1.21	0.55	-1.54	-3.12, 0.03	0.05
Age (in years)	0.02	-0.03, 0.74	0.45	0.02	-0.07, 0.12	0.66	-0.01	-0.71, 0.06	0.84
Unskilled labour	1.39	-0.12, 2.90	0.07	-0.29	-2.78, 2.20	0.81	2.36	0.49, 4.24	0.01
Semi-skilled	0.35	-0.98, 1.68	0.60	0.49	-1.41, 2.39	0.61	0.94	-0.92, 2.81	0.31
Poor vs non-poor	-0.36	-1.48-0.76	0.53	0.92	-0.80, 2.64	0.29	-0.32	-1.76, 1.11	0.65
Primary	1.17	-0.36-2.71	0.13	1.16	-1.41, 3.75	0.37	0.84	-0.96, 2.65	0.35
Secondary education	1.41	-0.56-3.39	0.16	2.20	-0.91, 5.31	0.16	-0.13	-2.70, 2.42	0.91

University	1.48	-1.78-4.74	0.37	0.99	-0.80, 2.64	0.65	0.32	-4.89-5.53	0.90
Diagnostic delay	0.01	-0.04-0.24	0.16	0.03	0.01, 0.05	0.002	-0.01	-0.22, 0.30	0.13
Total direct cots									
Males vs females	-1.71	-11.80, 8.38	0.73	-2.31	-20.29, 15.67	0.79	-3.58	-9.80, 2.63	0.25
Age (per year)	-0.01	-0.48, 0.46	0.97	0.28	-0.70,1.26	0.57	0.06	-0.19	0.31
Unskilled labour	1.80	-11.40, 15.01	0.78	-7.55	-33.38, 18.26	0.56	2.20	-5.18, 9.59	0.55
Semi-skilled labour	2.87-	-8.75,14.48	0.62	5.01	-14.66, 24.69	0.61	1.87	-5.49, 9.23	0.61
Poor vs non-poor	-2.34	-12.19,7.51	0.63	7.44	-10.42, 25.31	0.41	-2.40	-8.07, 3.27	0.40
Primary education	3.18	-10.21,16.56	0.47	8.96	-17.83, 35.76	0.66	0.66	-6.47, 7.78	0.85
Secondary education	6.12	-11.16, 23.40	0.48	20.86	-11.40, 53.12	0.20	4.22	-5.88, 14.32	0.40
University	9.36	-19.07, 37.84	0.51	10.53	-35.17, 56.25	0.64	-0.59	-21.14, 19.95	0.95
Diagnostic delay	0.04	-0.08, 0.16	0.52	0.52	0.34, 0.70	<0.001	-0.84	-1.32, -0.35	0.001
Total costs									
Males vs females	9.87	-26.39, 46.14	0.59	-4.98	-58.90, 48.93	0.85	-0.62	-44.96, 43.71	0.97
Age (per year)	0.34	-1.34, 2.03	0.68	-0.56	-3.50, 2.38	0.70	0.74	-1.06, 2.55	0.41
Unskilled labour	11.95	-35.50, 59.40	0.62	8.25	-69.18, 85.69	0.83	16.02	36.64, 68.69	0.54
Semi-skilled labour	30.47	-11.28, 72.23	0.15	58.81	-0.18, 117.81	- 0.05	26.64	-25.86, 79.14	0.31
Poor vs non-poor	0.89	-34.50, 36.31	0.96	8.39	-45.18, 61.98	0.75	2.39	-38.01, 42.81	0.90
Primary education	24.87	-23.25-72.98	0.31	19.73	-60.62, 100.09	0.62	18.06	-32.75, 68.88	0.48
Secondary education	69.54	7.43-131.65	0.02	69.45	-27.29, 166.19	0.15	46.10	-25.86, 79.14	0.20
University	108.89	6.6, 211.16	0.03	69.20	-67.87, 206.28	0.31	-15.74	-162.23, 130.73	0.83
Diagnostic delay	1.29	0.84, 1.73	<0.001	1.44	-19.56, -6.63	<0.001	-2.40	-5.86, 1.06	0.17

*****Estimated differences in median costs are presented with the corresponding 95% confidence intervals (95% CI); Diagnostic delay was defined as delay in seeking care three weeks or more after the onset of symptoms

Multivariable quintile regression was performed for median costs to examine the association of patient factors with the different types of costs. Separate models were run for direct, indirect and total costs.

[1] Reference: Unemployed

[2] Reference: no education.

Supplementary Table 3. Estimates of effects of different factors on median types of indirect and costs in USD among confirmed and presumptive TB patients.

Variable	All			Confirmed			Presumptive		
	Difference*	95% CI	P-value	Difference*	95% CI	P-value	Difference*	95% CI	P-value
Coping costs									
Males vs females	-0.24	-6.12,5.64	0.93	-3.86	-11.45, 3.71	0.31	-1.39	-12.58, 9.79	0.80
Age (in years)	0.02	-0.25,0.29	0.88	-0.25	-0.66, 0.16	0.23	0.15	-0.30, 0.61	0.51
Unskilled labour[1]	-2.38	-5.71,9.90	0.59	-8.56	-19.45, 2.33	0.12	-0.49	-13.78, 12.79	0.94
Semi-skilled[1]	-4.63	-11.41,2.14	0.17	-2.64	-10.94, 5.66	0.52	-5.01	-18.25, 8.24	0.45
Poor vs non-poor	0.30	-5.43,6.05	0.91	-2.56	-10.09, 4.98	0.50	2.09	-8.10, 12.28	0.68
Primary education[2]	2.09	-5.71,9.90	0.59	-2.89	-14.20, 8.40	0.61	5.92	-6.89, 18.74	0.36
Secondary education[2]	5.79	-4.28,15.86	0.25	-4.85	-18.46, 8.76	0.48	9.23	-8.94, 27.41	0.31
University[2]	-6.65	-23.24, 9.93	0.43	5.09	-14.19-24.37	0.60	-4.09	-41.05, 32.85	0.82
Diagnostic delay	2.47	0.87, 4.07	0.003	-0.04	-0.12, 0.03	0.26	-0.39	-1.27, 0.47	0.36
Less paid labour									
Males vs females	1.32	-2.69,5.33	0.51	3.78	-3.78, 11.35	0.32	0.74	-2.99, 4.46	0.69
Age (in years)	0.17	-0.01,0.35	0.07	0.19	-0.21, 0.60	0.34	0.15	-0.01, 0.30	0.05
Unskilled labour	2.80	-2.45,8.06	0.29	3.16	-7.71, 14.02	0.56	3.59	-0.83, 8.02	0.11
Semi-skilled labour	3.43	-1.18,8.06	0.14	1.44	-6.83, 9.72	0.36	4.63	0.22, 9.05	0.04
Poor vs non-poor	1.54	-2.37,5.57	0.43	-2.33	-9.85, 5.18	0.53	2.10	-1.29, 5.50	0.22
Primary education	3.15	-2.16,8.48	0.24	-2.51	-13.79, 8.77	0.65	4.38	0.11, 8.65	0.04
Secondary education	4.69	-2.17,11.57	0.17	-1.64	-15.22, 11.93	0.80	8.03	1.97, 14.08	0.01
University	3.88	-7.43,15.20	0.49	8.84	-10.40, 28.07	0.36	3.93	-8.37, 16.24	0.52
Diagnostic delay	0.09	0.05,0.15	<0.001	0.09	0.02, 0.17	0.01	-0.27	-0.56, 0.02	0.06
Decreased production									
Males vs females	3.12	-1.67,7.91	0.20	3.31	-4.73, 11.35	0.41	2.48	-4.39, 9.37	0.47
Age (in years)	0.11	-0.11,0.33	0.33	0.18	-0.25, 0.62	0.42	0.09	-0.19, 0.37	0.51
Unskilled labour	7.38	1.11,13.65	0.02	1.37	-10.19, 12.62	0.19	8.71	0.53, 16.89	0.03
Semi-skilled labour	6.40	0.89,11.92	0.02	5.16	-3.64, 13.97	0.24	7.25	-0.90, 15.40	0.08
Poor vs non-poor	-0.07	-4.75-4.60	0.97	0.08	-7.90, 8.09	0.98	-0.79	-7.07, 5.48	0.80

Primary education	2.25	-4.10,8.61	0.48	0.63	-11.36, 12.63	0.91	3.40	-4.49, 11.29	0.39
Secondary education	6.53	-1.67-,4.73	0.11	5.94	-8.49, 20.38	0.41	5.76	-5.42, 16.95	0.39
University	21.51	7.99,35.02	0.002	21.39	0.93,41.85	0.04	-4.33	-27.07, 18.42	18.41
Diagnostic delay	0.04	-0.02,0.09	0.20	0.05	-0.02,0.13	0.21	-0.17	-0.71, 0.36	0.51
Total indirect costs									
Males vs females	11.63	-11.37,34.63	0.32	6.60	-33.93,47.14	0.74	1.85	-34.74, 38.44	0.92
Age (per year)	0.38	-0.69,1.45	0.48	0.07	-2.14, 2.29	0.94	0.75	-0.74, 2.24	0.32
Unskilled labour	12.68	-17.41,42.78	0.40	14.47	-43.74,72.700	0.62	19.13	-24.32, 62.11	0.38
Semi-skilled labour	20.90	-5.58,47.38	0.12	37.24	-7.11, 81.60	0.09	22.94	-20.38, 66.27	0.29
Poor vs non-poor	6.29	-16.15,28.75	0.58	6.92	-33.36,47.20	0.73	5.82	-27.53, 39.18	0.72
Primary education	21.24	-9.27,51.75	0.17	8.96	-51.46, 69.37	0.76	20.17	-21.76, 62.11	0.34
Secondary education	61.52	22.14,100.92	0.002	54.24	-18.48,126.99	0.73	38.79	-20.65, 98.25	0.19
University	108.74	43.89,173.60	0.001	85.66	-17-40,188.72	0.10	-7.79	-128.66, 113.09	0.89
Diagnostic delay	0.46	0.12,0.74	0.001	0.56	0.16,0.98	0.007	-1.25	-4.09, 1.62	0.39
Total costs									
Males vs females	9.87	-26.39,46.14	0.59	-4.98	-58.90,48.93	0.85	-0.62	-44.96, 43.71	0.97
Age (per year)	0.34	-1.34,2.03	0.68	-0.56	-3.50,2.38	0.70	0.74	-1.06, 2.55	0.41
Unskilled labour	11.95	-35.50,59.40	0.62	8.25	-69.18,85.69	0.83	16.02	36.64, 68.69	0.54
Semi-skilled labour	30.47	-11.28,72.23	0.15	58.81	-0.18,117.81	0.05	26.64	-25.86-79.14	0.31
Poor vs non-poor	0.89	-34.50,36.31	0.96	8.39	-45.18,61.98	0.75	2.39	-38.01, 42.81	0.90
Primary education	24.87	-23.25,72.98	0.31	19.73	-60.62,100.09	0.62	18.06	-32.75, 68.88	0.48
Secondary education	69.54	7.43,131.65	0.02	69.45	-27.29,166.19	0.15	46.10	-25.86, 79.14	0.20
University	108.89	6.63,211.161	0.03	69.20	-67.87,206.28	0.31	-15.74	-162.23, 130.73	0.83
Diagnostic delay	1.29	0.84,1.73	<0.001	1.44	-19.56,6.63	<0.001	-2.40	-5.86, 1.06	0.17

*Estimated differences in median costs of are presented with the corresponding 95% confidence intervals (95% CI); Diagnostic delay was defined as delay in seeking care three weeks or more after the onset of symptoms. Multivariable quintile regression was performed for median costs to examine the association of patient factors with the different types of costs. Separate models were run for direct, indirect and total costs.

[1] Reference: Unemployed

[2] Reference: no education

4. Explaining patient delay in healthcare seeking and loss to diagnostic follow-up among patients with presumptive tuberculosis in Tanzania[2]

Grace Mhalu [1, 2,3]*, Mitchell G. Weiss [2,3], Jerry Hella [1, 2,3], Francis Mhimbira [1, 2,3], Enos Mahongo [1], Christian Schindler [2,3], Klaus Reither [2,3], Lukas Fenner [4], Elisabeth Zemp [2,3], Sonja Merten [2,3]

[1] Ifakara Health Institute, Dar es Salaam and Bagamoyo, Tanzania [2] Swiss Tropical and Public Health Institute, Basel, Switzerland [3] University of Basel, Switzerland [4] Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland

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Abstract

Background: Delay in healthcare seeking and loss to diagnostic follow-up (LDFU) contribute to substantial increase in tuberculosis (TB) morbidity and mortality. We examined factors, including perceived causes and prior help seeking, contributing to delay and LDFU during referral to a TB clinic among patients with presumptive TB initially seeking help at the pharmacies in Dar es Salaam Tanzania.

Methods: In a TB clinic, a semi-structured interview based on the explanatory model interview catalogue (EMIC) framework for cultural epidemiology was administered to presumptive TB patients enrolled at pharmacies during an intervention study. We assessed delay in seeking care at any medical care provider for a period of ≥3 weeks after the onset of symptoms, LDFU during referral (not reaching the TB clinic), and LDFU for three required TB clinic visits among the presumptive and confirmed TB patients. Logistic regression models were used to assess factors associated with delay and LDFU.

Results: Among 136 interviewed patients, 88 (64.7%) had delayed seeking care of which 59 (67%) were females. Eighty six patients (63.2%) were LDFU. Among the 50 (36.8%) non-LDFU, 26 (52.0%) had also delayed seeking care. Prior consultation with a traditional healer (aOR 2.84, 95% CI 1.08-7.40), perceived causes as ingestion (water and food) (aOR 0.38 CI 0.16-0.89), and substance use (smoking and alcohol) (aOR 1.45 CI 0.98-2.14) were all associated with patient delay. Female gender was associated with LDFU (aOR 3.80, 95% CI 1.62-8.87) but not with delay. Other conditions as prior illness and heredity were also associated with LDFU but not delay (aOR 1.48 CI 1.01-2.17).

Conclusion: Delay and LDFU after referral from the pharmacies were substantial. Notable effects of female gender indicate a need for more attention to women's

health to promote timely and sustained TB treatment. Public awareness to counter misconceptions about the causes of TB is needed.

4.1 Introduction

Tuberculosis (TB) ranks above HIV/AIDS as the number one infectious-disease killer worldwide accounting for 1.7 million TB deaths and 10.4 million new cases in 2016 (WHO, 2017). Tanzania is among the 30 countries with a high TB burden where TB case detection relies on passive case findings. Although Individuals with TB symptoms may present themselves to healthcare facilities for TB diagnosis (Ministry of health and social welfare, 2006b; Senkoro M, Hinderaker SG, Mfinanga SG, 2015; WHO, 2015c) the problem of delayed appropriate help seeking for people with TB symptoms is widespread in sub-Saharan African countries (Sreeramareddy C.T, Panduru K.V, Menten J, Ende J.V, 2009b). The problem of diagnosis and starting appropriate treatment is further complicated by early loss to diagnostic follow up (E. Botha et al., 2008). In view of good prospects for cure with timely diagnosis and treatment, these are serious problems [2, 6].

Diagnosis and treatment of TB patients require recognition of symptoms and both prompt presentation for diagnosis and treatment in a competent healthcare facility. Furthermore, healthcare must be sustained to limit morbidity and mortality (MacPherson et al., 2014b; Shete et al., 2015). People with symptoms of TB usually follow a complex pathway to care, typically including prior consultation with two or three healthcare providers before reaching specialized healthcare facilities capable of diagnosing and treating TB (Mfinanga and Mutayoba, 2008b; Mhalu et al., n.d.; Eliud R. Wandwalo and Mørkve, 2000b). Research suggests that factors contributing to delay in reaching specialized healthcare facilities and loss to diagnostic follow-up (LDFU) include dissatisfaction with health services, use of self-prescribed medication and initial help seeking with traditional healers (Hinderaker et al., 2011a; Khan et al., 2009; Rabin et al., 2013). LDFU leads to poor health outcomes for the individuals

such as increased morbidity, decreasing the quality of life and increasing mortality (Fatima et al., 2015b). It also enables further spread of TB.

Most studies addressing loss to follow-up (LTFU) consider TB patients in treatment, but little is known about LDFU for the larger group of people with presumptive TB symptoms who have not yet been diagnosed and not yet started treatment (Fatima et al., 2015b; Wali A, Kumar A.M.V, Hinderaker S.G, Heldal E, Qaader E, Fatima R, 2015). To explain delayed healthcare seeking and LDFU that complicates diagnosis and initiating TB treatment, we examined the role of selected features of patients' own illness explanatory models, including patient-perceived TB causes and prior healthcare seeking (Gosoniu et al., 2008b). We interviewed people with symptoms of TB who were referred for diagnosis but did not come for the three recommended follow-up visits and assessed patient delay in seeking care, and we compared them with TB patients who completed recommended diagnostic follow-up in a TB referral clinic in Dar es Salaam Tanzania, to identify factors associated with delay and LDFU.

4.2 Methods

Study setting

Intervention study: Tuberculosis case findings at the pharmacies

A study of TB case finding at pharmacies (TB-PHARM) was conducted in 2015 in the Ilala district of Dar es Salaam, Tanzania. Trained pharmacists who used an electronically monitored referral system participated in the study (Mhimbira F, Hella J, Mutayoba B, Mahongo E, Minde J, n.d.). The study aimed at developing and evaluating referrals of presumptive TB patients from pharmacies to TB clinics of the National Tuberculosis and Leprosy Programme (NTLP). Selection of the pharmacies was based on the geographical location to the TB clinic, the ownership (government, private) and the size of the pharmacy to obtain a representative mix. The intervention study included all pharmacy clients aged 18 years or older visiting selected pharmacies in the Ilala district with TB symptoms (coughing of any duration) as well as pharmacy clients who bought antibiotics for patients with cough symptoms at home. Identified presumptive TB patients were counseled and referred to a TB diagnostic centre with a referral card. The patient flow of the intervention study is schematically shown in Figure 11. Individuals who were currently investigated for TB, as well as TB patients on treatment or who had completed treatment within the last three months were excluded from the intervention study.

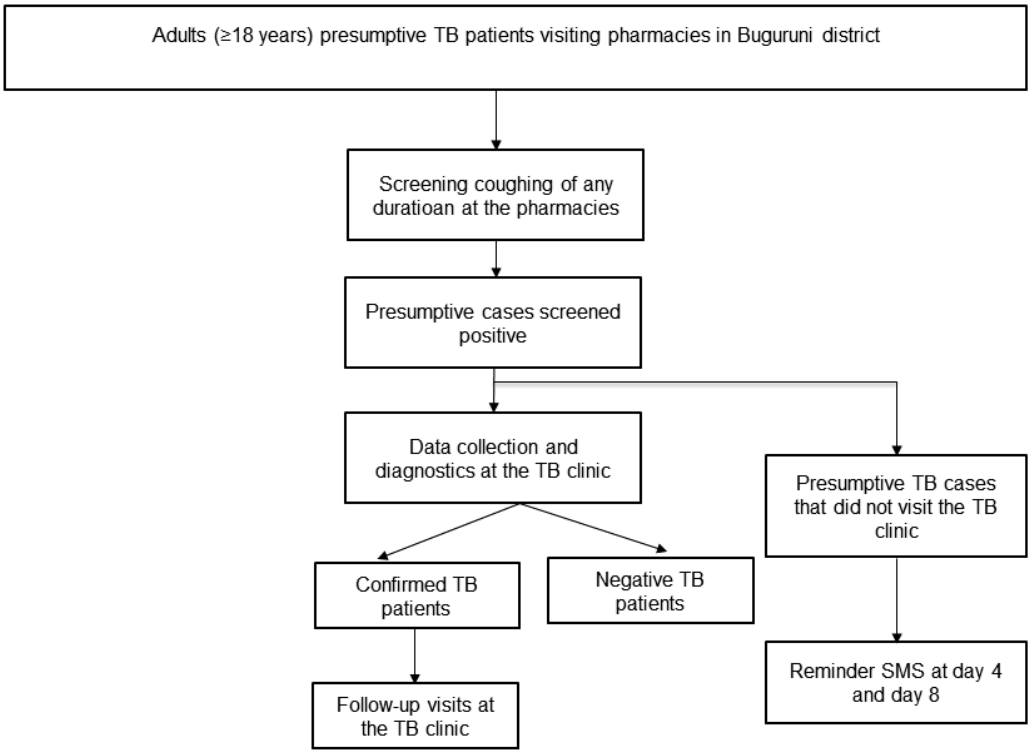

Figure 11. Intervention study (TB-PHARM) patient referral flowchart

Short overview of LDFU sub-study

The LDFU sub-study included a fraction of the presumptive and confirmed patients that participated in the big TB-PHARM study. This was an exploratory study that aimed at exploring factors associated with patient delay and loss to diagnostic follow-up in the intervention study (TB-PHARM).

LDFU-study setting

The LDFU sub-study was conducted in Ilala district (Buguruni hospital) in Dar es Salaam Tanzania. Ilala has a population of 1,220,611 with an average household size of 4.0 persons (Tanzania census of 2012). The district notified 4,582 TB cases (all forms) in 2012. The study setting was a residential area in Buguruni sub-district with a population of 70,585 and 559 notified TB cases in 2012. There is one registered TB diagnostic and treatment centre in the study area.

Study population

We established a patient tracing system that included community health workers, Ex-TB patient's organisations and clinical workers. We traced all presumptive and confirmed TB patients who did not visit the TB clinic after referral from the pharmacies or those who did not complete their required three visits at the clinic after treatment initiation. The list of all LDFU was obtained from the main database of the intervention study. We further included confirmed TB patients from the main database of the intervention study who were not LDFU and completed all the required three visits at the TB clinic. Patient delay was assessed in all the LDFU and non-LDFU patients and was defined as delay to visit a healthcare provider including pharmacies, hospitals, dispensaries and primary healthcare centers of three weeks or more after the onset of symptoms.

Instrument

We used a mixed method approach in a semi-structured explanatory model interview based on the framework of the explanatory model interview catalogue (EMIC) for cultural epidemiology to study patients' illness explanatory models (Weiss, 2001; Weiss MG, 1997). The interview and coding categories were adopted from an EMIC interview developed and used in a WHO/TDR-supported multi-country study of gender and tuberculosis in India, Bangladesh, Malawi and Colombia (Weiss et al., 2006). The various sections of the interview inquired about priority symptoms, perceived causes (PCs) and place and timing of help seeking including delay. Open questions were asked first, and responses were coded according to coding options. Spontaneously reported categories in response to open questions were distinguished from elicited responses to probed categories that had not been mentioned spontaneously. Narrative elaboration was included as a qualitative

component of the data set. Additional questions were asked about the most important categories of perceived causes and health-seeking. Patient delay was assessed by asking the patients regarding the interval between the onset of symptoms to consultation with any healthcare provider.

Each section of the EMIC began with a short introduction to help the respondents understand the study interests and questions and to encourage them to respond candid and to speak freely (Weiss MG, 1997). The instrument was prepared in English and translated into the local language (Swahili). Patients' narrative interview data were translated into English for analysis.

Variables

Outcome variables

Delay in seeking health care was regarded as an outcome variable. Patient delay was defined as a duration of three weeks or more between onset of any TB-related symptom (such as coughing, chest pain, fever, weight loss, and hemoptysis) and presentation to any healthcare facility including pharmacies, hospitals, primary healthcare facilities as well as dispensaries.(World Health Organization, 2009). The cutoff point for patient delay of three weeks was considered sufficient as described in previous studies (Said et al., 2017).

Furthermore, LDFU was regarded as outcome variable. LDFU was defined as failure to present after referral from the recruitment pharmacy to the TB clinic (pharmacy LDFU) within two months or failure to return for all three required diagnostic visits after recruitment in the TB clinic (clinic LDFU). Negative and confirmed TB patients who came for timely assessment to all three diagnostic visits were classified as non-LDFU. LDFU was dichotomized as 1 (non-LDFU) or 0 (LDFU).

Explanatory variables

Socio-cultural variables specifying features of illness explanatory models included perceived causes that encompass locally held beliefs regarding the common causes of TB. Treatment-seeking referred to the type of healthcare provider patients may consult, including traditional medical practitioners, pharmacies and hospitals (Weiss et al., 2008b). Additionally, sex, age, and socio-economic variables (e.g., education and occupation) were considered as explanatory variables.

A prominence score was assigned to each of the EMIC variables denoting perceived causes and help-seeking options. Prominence was based on whether and how a respondent reported each category. We assigned a value of 2 for a spontaneous response, a value of 1 for a positive response only after probing the category and a value of 0 if the category was still not reported by the respondent when probing. Furthermore, a value of 3 was assigned to those categories that were identified as most important perceived cause or treatment seeking option. This value of 3 was added to the value for how a category was reported (0, 1 or 2). Thus, the values of the prominence score variable had a theoretical range of 0 to 5.

Data collection

Clinical officers with research experience administered the interviews after two weeks of training. Two clinical officers were present for each interview; one interviewed the patient and the other served as scribe, taking notes. They changed roles in successive interviews. Interviews required 30 to 60 minutes, and data were collected on paper interview forms.

Data analysis

Categorical and numerical variables from the EMIC interviews were double entered using Epi Info (Centre for Disease Control and Prevention, Atlanta GA, USA, version

7). We cleaned the data and performed statistical analysis using Stata version 14.2 (StataCorp, College Station, TX, USA). We calculated the frequencies of response options and of the derived prominence score values of categories of perceived causes of TB and categories of treatment seeking (Weiss MG, 1997), analysing mean prominence for the comparison groups.

In a separate analysis, we grouped categories representing details of a common theme as in previous studies (Merten et al., 2013). For example, perceived cause (PC) response variables for water and food as perceived causes were grouped under ‘ingestion’, a PC group variable. PC response variables for alcohol and smoking were grouped under ‘substance use’. Interview-coded response variables for climate, dust, contamination and airborne illness were all grouped under ‘environmental causes’. Response categories including evil eye/sorcery, demons and the will of god were included in a PC group labeled ‘magico-religious’. A PC group variable labelled ‘contact’ referred to both sexual contact and casual contact with an infected person. A PC group ‘other’ included response categories for heredity, conditions such as fatigue, working too hard and carrying heavy loads (these were explained by some as possibly causing chest pain which later develops into TB). Prominence score values for PC group variables were derived by computing the maximum prominence for each PC response variable in the PC group (0=not mentioned, 1=mentioned on probe, 2=mentioned spontaneously, additional value of 3 if any category in the group had been identified as most important perceived cause). In case of non-linear associations with the outcome the variable was transformed into a categorical variable and included as such in the logistic regression model. To assess the statistical significance of differences between PC response variables, PC group variables and help seeking (HS) response variables

for the two sets of comparison groups, i.e., for patient delay and LDFU, we used the Wilcoxon rank sum statistical test.

To examine the factors associated with delay and LDFU, we conducted univariate and multivariate logistic regressions. Variables for categories of PC, treatment seeking, and socio-economic factors were summarized with univariate statistics. Multivariate logistic regression models were first run for each subcategory of questions about perceived causes and treatment seeking while adjusting for socio-economic variables. Prominence scores were treated as covariates and linearity of their association with the logit of delay and LDFU was tested by including a quadratic term. Significant non-linearity was only found for ingestion and this variable was then dichotomized into 0 vs. 1-5. Only variables which were associated with the outcome variable with a p-value <0.2 were retained in the final multivariate model except for the variables of perceived causes. We then tested each retained variable for interaction with sex and presented the respective gender-specific estimates.

Qualitative data for the integrated analysis

To explain identified differences and associations of the explanatory variables, we analysed narrative data. Narratives from the EMIC interviews were coded and imported in MAXQDA version 12 (VERBI Software, Berlin, Germany). The narratives from EMIC were initially thematically coded with reference to interview questions eliciting the narrative. We used the framework method of Gale et al (Gale KN, Heath G, Cameron E, Rashid S, 2013a) for analysis of the qualitative data. The analysis identified emerging themes, patterns, similarities and differences.

Open coding to label concepts were used to define and develop categories, based on properties and dimensions of the respondent's description (Strauss A, 1998). We developed and assigned a list of thematic codes that correspond to each separate

section of the EMIC interview (PC, HS, as well as study-specific issues) (Weiss et al., 2006).

4.3 Results

Sample characteristics

The study population includes 136 presumptive and confirmed TB patients. Out of these, patients delay of three weeks and more after the onset of symptoms was present in 88 (64.7%) patients, of which 59 (67%) were females. Overall, 86 (63.2%) were LDFU from pharmacies and TB clinic, and 50 (36.8%) were non-LDFU (confirmed or negative TB patients) (Table 6). Among the 86 patients who were LDFU, 26 (30.2%) did not complete all of the three diagnostic visits at the TB clinic (clinic LDFU). Furthermore, 34 patients in the LDFU group could not be traced and included in the study (Figure 12). Additionally, in the LDFU group patient delay of three weeks and above was present in 62 (72.1%) patients. The median age was 32 years (Interquartile range [IQR]: 27-40 years). 82 (60.3%) of the respondents were females.

Table 6. Baseline characteristics of the respondents

Characteristic n (%)	All n=136	Non-LDFU[a] n=50	Delay[b] n=88	LDFU[c] n=86
Age in years, median (IQR)	32 (27-40)	32 (26-36)	32 (26-40)	33 (28-40)
Age group, years				
18-27	35 (25.7)	14 (28.0)	24 (27.2)	21 (24.4)
28-37	57 (42.0)	24 (48.0)	35 (39.8)	33 (38.4)
≥ 38	44 (32.3)	12 (24.0)	29 (33.0)	32 (37.2)
Sex				
Male	54 (39.7)	28 (56.0)	29 (33)	26 (30.2)
Female	82 (60.3)	22 (44.0)	59 (67)	60 (69.8)
Level of education				
Primary/Secondary	118 (86.8)	46 (92.0)	74 (84.1)	72 (83.7)
No formal education	18 (13.2)	4 (8.0)	14 (15.9)	14 (16.3)
Religion				
Muslim	88 (64.7)	32 (64.0)	59 (67)	56 (65.1)
Christian	48 (35.3)	18 (36)	29 (33)	30 (34.9)
Employment status				
Unemployed	36 (26.5)	15 (30)	27 (30.7)	21 (24.4)
Employed	100 (73.5)	35 (70)	61 (69.3)	65 (75.6)
Monthly household income				
Low income	46 (33.3)	17 (34.0)	34 (38.6)	35 (40.7)
Middle income	50 (36.7)	18 (36.0)	29 (32.9)	25 (29.1)
High income	40 (29.4)	15 (30.0)	25 (28.4)	26 (30.2)
Household size				
≤4	75 (55.2)	27 (54)	45 (51.1)	48 (55.8)
>4	61 (44.8)	23 (46)	43 (48.9)	38 (44.2)

IQR: Interquartile Range; LDFU: loss to diagnostic follow-up; Non-LDFU: non- loss to diagnostic follow-up; 1 US $=2,190 Tanzanian Shillings

[a] Including negative and confirmed TB patients who attended the clinic and completed all the visits;

[b] Patients who delayed seeking health for ≥3 weeks after onset of symptoms in both LDFU and non-LDFU groups;

[c] Including patients who did not visit the clinic after referral from pharmacy and those who did not complete their visits after treatment initiation

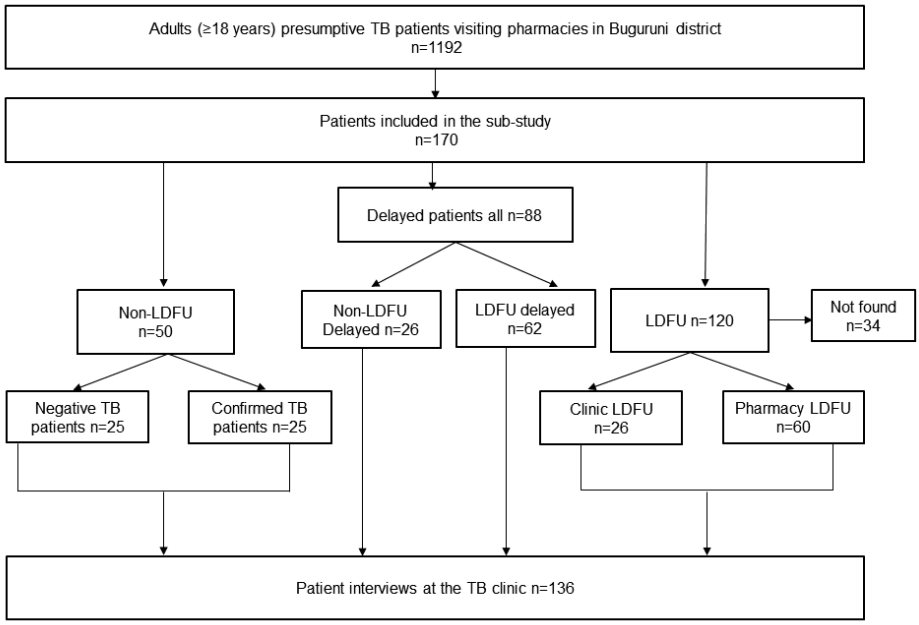

Figure 12. Flowchart of the patient selection (LDFU sub-study)

Most of the study participants had primary education (86.8%) and were Muslims (64.7%). Patients who had a middle monthly household income were slightly more frequent (36.8%) than those who had low (33.3%) and upper (29.4%) household income.

Perceived causes

Dust was considered to be a main cause of TB symptoms. 47.7% in the LDFU group and 54.0% in the non-LDFU group spontaneously mentioned dust as the cause of TB symptoms (Table 7).

“I work in the marketplace. My working environment is full of dust; I think this is what caused me to develop TB symptoms.” *(male, 41 years).*

This was followed by evil eyes and sorcery, 45.3% and 28.0%, respectively. Other common explanations mentioned of TB symptoms were climate, demons or gods.

“My illness might have been caused by the environment at my previous work. As a cook, I was exposed to a lot of smoke and heat. Moreover, my workplace was near a dusty road. Therefore, I was exposed to dust as well. I strongly believe that was the cause of my illness”*. (male, 27years).*

“I work at the market where I often generate more profit than most of my surrounding neighbours. I began coughing blood and became very fragile, I thought my neighbours were jealous of my success and bewitched me. I visited a traditional healer”. *(female, 44 years).*

In contrast; alcohol was rarely mentioned spontaneously as a cause of TB symptoms. 51.2% and 36% in LDFU and the non-LDFU group mentioned alcohol as a perceived cause of the disease after probing. This was followed by smoking in both groups (48.8% and 46.0%). Prior illness and contaminated water were reported as the main causes of the disease after probing

.

Table 7. Perceived causes for TB symptoms among LDFU and non-LDFU patients

	LDFU n=86 How reported[a]					Non-LDFU n=50 How reported[a]				
Category[a]	Total reported %	Spont %	Probe %	Most important %	Mean Prominence[b]	Total reported %	Spont %	Probe %	Most important %	Mean Prominence[b]
Ingestion	36.0	5.8	30.2	4.6	0.6	58.0	12.0	50.0	8.0	0.9
Food	24.4	4.7	19.8	3.5	0.4	44.0	6.0	38.0	6.0	0.6
Water	27.9	1.2	26.7	1.2	0.3	32.0	6.0	26.0	2.0	0.4
Substance use	88.3	24.4	63.9	16.3	1.6	84.0	22.0	62.0	10.0	1.3
Alcohol	56.9	5.8	51.2	4.7	0.8	44.0	8.0	36.0	2.0	0.6
Smoking	69.7	20.9	48.8	11.6	1.3	66.0	20.0	46.0	8.0	1.1
Environmental causes	97.7	82.6	15.1	45.4	3.2	98.0	84.0	14.0	44.0	3.1
Climate	74.4	38.4	36.1	6.9	1.3	86.0	46.0	40.0	4.0	1.4
Dust	75.6	47.7	27.9	18.6	1.8	86.0	54.0	32.0	28.0	2.2
Contamination	69.8	27.9	41.8	5.8	1.1	56.0	10.0	46.0	2.0	0.7
Airborne illness	48.8	19.8	29.1	13.9	1.1	40.0	6.0	34.0	10.0	0.8
Magico-religious courses	93.0	70.9	22.0	15.1	2.1	98.0	62.0	36.0	14.0	2.0
Evil eye/sorcery	80.2	45.3	34.9	13.9	1.6	70.0	28.0	42.0	12.0	1.3
Demons or Gods	80.2	45.4	34.9	1.2	1.2	78.0	48.0	30.0	2.0	1.3
Contact	68.6	24.4	44.2	5.8	1.1	62.0	14.0	48.0	8.0	1.0
Casual sexual contact	22.1	5.8	16.3	2.3	0.3	34.0	2.0	32.0	2.0	0.4
Contact with infected person	62.8	20.9	41.9	3.5	0.9	50.0	12.0	38.0	6.0	0.8
Other conditions	68.6	24.4	44.2	10.5	1.2	78.0	24.0	54.0	8.0	1.3
Prior illness	27.9	1.2	26.7	5.8	0.4	38.0	4.0	34.0	4.0	0.5
Heredity	51.2	19.7	31.4	3.5	0.8	60.0	20.0	40.0	4.0	0.9
Others	17.4	3.5	13.9	1.2	0.2	34.0	2.0	32.0	0	0.4

LDFU: loss to diagnostic follow-up; Non-LDFU: non- loss to diagnostic follow-up, [a] Columns indicate percentage of reported categories and whether a category was identified as most troubling; [b] Mean prominence based on values assigned to each reported category (0 = not reported, 1= reported after

probing, 2=reported spontaneously 3 = identified as most troubling 4= most troubling and reported after probing 5= most troubling and reported spontaneously

Treatment seeking

Respondents were asked about their healthcare seeking after onset of symptoms. Seeking help from the pharmacies was considered the most important choice after the onset of symptoms for both females and males in LDFU (Table 8) and non-LDFU groups (Table 9).

“I belived that the pharmacist would understand what is my problem .She gave me some tablets to relieve pain and informed me it would be best to go to the clinic”. *(female 57 years).*

Furthermore, among help-seeking options, use of traditional healers was mentioned in both groups, including 21.7% of women and 23.1% of men in the LDFU group and 22.7% women and 32.1% men in the non-LDFU group. Seeking help from religious healers was reported as most important choice among men in the LDFU group compared to women (11.5% vs 6.7%) while in non-LDFU group women reported help-seeking from religious leaders more often as the most important choice compared to men (9.1% vs 3.6%). Furthermore, the majority of those who used religious healers in both groups were Muslims. Narrative elaboration suggests psychological comfort was valued from visiting a traditional healer, especially among women. Other health-seeking practices, such as seeking care at dispensaries and TB clinics, were mentioned less often by both groups of respondents.

“I feel safer to visit a traditional healer. I will rather go to a traditional healer than to the hospital. Doctors at the hospital sometimes mismanage patients”. *(female, 27 years).*

Table 8. Treatment seeking for TB symptoms among women and men in the LDFU group

LDFU women n=60						LDFU men n=26					
	How reported[a]					How reported[a]					
Category[a]	Total reported %	Spont %	Probe %	Most important %	Mean Prominence[b] %	Total reported%	Spont %	Probe %	Most Important %	Mean Prominence[b]	
Home remedies	83.3	45.0	38.3	15.0	1.7	80.7	23.1	57.6	3.8	1.1	
Pharmacy	96.7	86.7	10.0	36.7	2.9	92.3	65.4	26.9	38.5	2.7	
Hospital	48.3	15.0	33.3	11.7	0.9	46.1	11.5	34.6	3.9	0.6	
Traditional healer	76.6	53.3	23.3	21.7	1.9	76.9	42.3	34.6	23.1	1.9	
Religious healer	40.0	11.7	28.3	6.7	0.7	42.3	11.5	30.8	11.5	0.8	
Dispensary	33.3	8.3	25.0	0	0.4	34.6	23.1	11.5	7.7	0.6	
TB clinic	10.0	6.7	3.3	6.7	0.4	23.1	3.8	19.2	3.8	0.3	*

LDFU: loss to diagnostic follow-up; [a] Columns indicate percentage of reported categories and whether a category was identified as most troubling; [b] Mean prominence based on values assigned to each reported category (0 = not reported, 1= reported after probing, 2=reported spontaneously 3 = identified as most troubling 4= most troubling and reported after probing 5= most troubling and reported spontaneously

Table 9. Treatment seeking for TB symptoms among women and men in Non-LDFU group

Non-LDFU women n = 22						Non-LDFU men n = 28					
	How reported[a]					How reported[a]					
Category[a]	Total reported %	Spont %	Probe %	Most important %	Mean Prominence[b]	Total reported%	Spont %	Probe %	Most Important %	Mean Prominence[b]	
Home remedies	86.3	54.5	31.8	9.1	1.6	75.0	32.1	43.0	14.3	1.5	
Pharmacy	81.8	40.9	40.9	27.3	2.0	96.4	75.0	21.4	28.6	2.6	*
Hospital	68.2	36.4	31.8	4.6	1.2	71.4	50.0	21.4	7.1	1.4	
Traditional healer	81.8	36.4	45.5	22.7	1.7	67.9	39.3	28.6	32.1	2.0	
Religious healer	59.1	13.6	45.5	9.1	1.0	39.3	3.6	35.7	3.6	0.5	
Dispensary	40.9	18.1	22.7	0	0.5	42.8	7.1	35.7	3.6	0.6	
TB clinic	22.8	4.6	18.2	9.1	0.5	21.4	3.6	18.0	0	0.3	

Non-LDFU: non- loss to diagnostic follow-up, **[a]** Columns indicate percentage of reported categories and whether a category was identified as most troubling; [b] Mean prominence based on values assigned to each reported category (0 = not reported, 1= reported after probing, 2=reported spontaneously 3 = identified as most troubling 4= most troubling and reported after probing 5= most troubling and reported spontaneously

Patterns of distress

Coughing was reported by 89.5% vs 88% of patients of the LDFU and non-LDFU as a major distress associated with the experience of having TB, followed by fever 73% *vs* 58% respectively. Respondents in both groups rarely mentioned other symptoms such as weight loss, breathlessness, and chest pain.

The narratives suggested that coughing blood (hemoptysis) was a pattern of distress that led to eventually seeking help at the pharmacies and other healthcare facilities.

"I had a low fever and mild cough for a week. I purchased some antibiotics at the pharmacy. Yet I did not feel better and later I started noticing blood in my sputum. I thought it was serious and decided to visit the hospital for more check-ups". *(male, 40 years).*

Additionally, coughing blood was associated with socially enacted stigma. Several narratives indicated the manifestation of stigma to the presumptive TB cases as a result of their symptoms.

"My colleagues were frightened with my condition which included fever and coughing blood. One day they explicitly mentioned that they no longer wanted to stay with me because I was coughing blood" (female, 51 years).

Factors associated with delay in seeking healthcare

We examined which categories of PC and HS were associated with delay in seeking care after adjusting for socio-demographic and socio-economic variables. In the multivariate analysis, diagnostic delay of ≥3 weeks was positively associated with a mid-range household monthly income (compared to low income) (aoR 3.35 95% CI 1.21-9.21), unemployment (aoR 2.81 95% CI 1.00-7.90), and seeking help from a traditional healer (aOR 2.66 95% CI 1.03-6.84) (Table 10). Additionally, the odds of patient delay for females were higher than for males, (aoR 2.16 95% CI 0.96-4.84). We also observed a positive association with perceived substance use as a cause of

TB, which was however not statistically significant. (aoR 1.41 95% CI 0.96-2.06). The association with perceived cause ingestion was not linear, with a significantly reduced risk of delay among patients with prominence scores between 1 and 5 compared to those with a score of 0 (aOR=0.41; 95% CI: 0.18-0.93). This is underscored by the following quotes:

"I described my symptoms to my colleague. His advice was to consult a traditional healer. The traditional healer prescribed some medications to use for a month and re-visit him after completion. My condition worsened after using the traditional medicines for more than two weeks. I decided to visit the pharmacy". (*female, 35 years).*

Financial hardship was also mentioned as a reason for diagnostic delay and seeking help at the traditional healers.

“I am from a less privileged family. I could not afford the treatment expenses at the hospital. Traditional healers are cheaper compared to hospitals and other health facilities. *(male, 29 years).*

“I stayed for two months before going to the pharmacy. I just used grinded ginger for my symptoms. The reason was I did not have enough money. If I had enoughn money I would have gone earlier to the pharmacy.” *(female 26 years).*

Another factor mentioned by the respondents for the diagnostic delay was substance use example smoking.

“I used to smoke a lot. I stopped because my wife did not like the behaviour. When I started coughing, I thought it was the aftermath of my behavior. I thought since I stopped, the cough will also disappear however it did not. My condition worsened then I decided to visit the traditional healer” *(male 27 years).*

Another factor commonly mentioned by the respondents for the diagnostic delay was the perception of coughing as a ‘normal’ cough. A female respondent said:

“My experience of coughing frequently made me feel it was a normal cough that will eventually disappear with some antibiotics. I took antibiotics for almost a month nevertheless my condition worsened. I visited the pharmacy” (female, 39 years).

Table 10. Multivariate analysis of factors associated with delay after onset of symptoms for presumptive and confirmed TB patients, n=136

Variable	aOR	P-value	95% CI
Sex			
Male	1 (Ref)		
Female	2.16	0.06	0.96-4.84
Monthly household income			
Low income	1 (Ref)		
Middle Income	3.35	0.01	1.21-9.21
High Income	2.18	0.14	0.77-6.17
Occupation			
Employed	1 (Ref)		
Unemployed	2.81	0.05	1.00-7.90
Perceived causes			
Ingestion			
0	1 (Ref)		
1-5	0.41	0.03	0.18,0.93
Magico-religious	1.11	0.56	0.76-1.63
Environmental causes	1.09	0.57	0.79-1.50
Substance use	1.41	0.07	0.96-2.06
Person to person contact	0.93	0.73	0.64-1.36
Other conditions	1.01	0.94	0.70-1.45
Help-seeking			
Traditional healers	2.66	0.04	1.03-6.84
Religious healer	1.67	0.23	0.71-3.87

CI=95% Confidence Interval; Delay was defined as three weeks or more after onset of symptoms up to the visit of the TB clinic, OR, Odds ratio. Odds ratio associated with variables of perceived causes refer to a unit increment in the respective variable except for ingestion which showed a non-linear association with delay and was therefore categorized. All the variables listed were included simultaneously in the model.

Factors associated with LDFU

Women were significantly more likely to be lost to diagnostic follow-up (aoR 4.12, 95% CI: 1.78-9.50). The perceived cause “other conditions”, including prior illness, was positively associated also with LDFU (aoR 1.39 95% CI 0.96-2.02) (Table 11). The association between LDFU and perceived cause ingestion was also non-linear, with a significantly reduced risk of LDFU among patients with prominence scores between 1 and 5 compared to those with a score of 0 (aOR=0.31; 95%.CI: 0.14, 0.70). When stratifying analyses by gender, all odds ratios were larger among women but none of the differences between the gender-specific estimates was statistically significant (Table 12).

Variations in the profile of men and women on reason for LDFU were apparent in the narratives. While women were more concerned with the financial burden to their spouses and family members, men were worried about financial burden resulting from missing work.

“The pharmacist advised me to seek further help for my symptoms at the hospital. I decided not to. I did not want to impose more financial burden to my husband and family as a result of my condition”. *(female, 44 years).*

“I was not concerned with the costs of treatment at the hospital. I was more worried that my boss will not understand me if I ask permission to visit the hospital” *(male 41 years).*

Fear of being diagnosed with TB in relation to HIV was recurring from the narratives as well as fear of isolation if diagnosed with TB, although it was not statistically significant in the quantitative analysis.

"The pharmacist gave me a small card to come for further check-ups. I was afraid to be asked to test for HIV. I was not ready to know my HIV status*”. (male 25 years).*

“My friend was diagnosed with TB and people were afraid to even eat with him. I thought it would be the same with me that’s why I did not visit the hospital as advised at the pharmacy.” *(female 21 years).*

Table 11. Multivariate analysis of factors associated with LDFU for presumptive and TB patients, n=136

Variable	aOR	P-value	95% CI
Sex			
Male	1 (Ref)		
Female	4.12	0.001	1.78-9.50
Perceived causes			
Ingestion			
0	1 (Ref)		
1-5	0.31	0.005	0.14, 0.70
Magico-religious	1.29	0.18	0.88-1.91
Environmental causes	1.06	0.68	0.78-1.43
Substance use	1.26	0.19	0.88-1.80
Person to person contact	1.13	0.51	0.77-1.66
Other conditions	1.39	0.08	0.96-2.02
Help-seeking			
Traditional healers	1.39	0.48	0.54-3.59
Religious healer	0.51	0.11	0.22-1.17
Hospital	0.54	0.15	0.23-1.24

CI=95% Confidence Interval; OR, Odds ratio LDFU: loss to diagnostic follow-up. Odds ratio associated with variables of perceived causes refer to a unit increment in the respective variable except for ingestion, which showed a non-linear association with LDFU and was therefore categorized. All the variables listed were included simultaneously in the model

Table 12 Multivariate analysis of factors associated with LDFU for presumptive and TB patients with gender specific estimates, n=136

Variable	Females aOR (95% CI)	Males aOR (95% CI)	P-Value (Interaction)
Perceived causes			
Ingestion	0.50	0.16	0.54
Environmental causes	1.17	0.84	0.24
Magico-religious	1.96	0.97	0.14
Substance use	1.48	1.02	0.29
Person to person contact	1.46	0.76	0.99
Other conditions	2.14	0.80	0.14
Help-seeking			
Traditional healers	2.55	0.63	0.40
Religious healer	0.84	0.14	0.14
Hospital	1.47	0.14	0.11

OR, Odds ratio; 95% CI= 95% Confidence Interval. LDFU: loss to diagnostic follow-up; Gender-specific odds ratios were obtained from model including gender-specific terms for the respective variable in addition to the other variables listed in the table.

4.4 Discussion

Results from this study indicate that patient delay of ≥3 weeks after the onset of symptoms was observed in almost two third, of the respondents. LDFU from the pharmacies to the TB clinic was observed in 44.1% of the presumptive patients, and a third of the patients who did reach the centre, did not complete all required visits. Pharmacies and traditional healers were main healthcare facilities for treatment seeking after the onset of symptoms.

Seeking care at healthcare facilities with absence or sub-optimal TB diagnostics before reaching TB centers was associated with patient delay. This finding indicates that presumptive TB patients follow a complex pathway to care before reaching suitable healthcare facilities for TB diagnosis and treatment. Undoubtedly, this suggests that a substantial number of presumptive TB patients delay seeking appropriate care as a result of visiting non-professional healthcare providers before TB diagnosis (Auer et al., 2000b; Getnet et al., 2017b; Eliud R. Wandwalo and Mørkve, 2000b). Consequently, this leads to delay in seeking healthcare after the onset of symptoms.

Women reported being comfortable with the care provided by the traditional healers and that healthcare workers would sometimes mistreat patients in the hospitals. This might indicate abuse and low quality of care in public health facilities in addition to a client's need for psychological comfort. This finding is in line with research documenting that women reach clinical treatment services through a circuitous route and prefer seeking healthcare from traditional healers and private practitioners (Eastwood and Hill, 2004b; Johansson et al., 2000a) instead of directly seeking care at healthcare facilities.

Presumptive patients with middle monthly household income delayed more compared to those with low and high incomes. Possibly, presumptive patients who

fell in this group had a higher preference for visiting non-professional healthcare professionals than those with upper and low monthly household income. Furthermore, we believe that these patients used self-medication more frequently after the onset of symptoms which is among determinants of delay as reported elsewhere (Bonadonna et al., 2017). Moreover, financial limitations resulting from unemployment were related to patient delay. The economic burden associated with treatment seeking is high for the poor population, which is most at risk of acquiring TB, which has already been noted in other settings (Nissen et al., 2012; Tadesse et al., 2013b; Thorson et al., 2000b). This highlights the need for poverty reduction in marginalized communities that will consequently contribute to the reduction of TB in low-resource settings especially in sub-Saharan countries (Barter et al., 2012b; WHO, 2004).

Furthermore, non-reporting of food or water as potential cause of TB was associated with an increased risk of patient delay. This finding may indicate a tendency of presumptive and TB patients to attribute their TB symptoms to other causes than food and water which in turn lead to early health-care seeking. Our findings contradict findings from a recent study in India that found that attribution of TB symptoms to factors such as water, pollution and cold favoured diagnostic delay in the TB patients (Mistry et al., 2016).

Our results show that seeking help at the traditional healers was associated with delay. One of the factors associated with seeking care at traditional healers was financial constraint. Patients claimed that traditional healers are cheaper than other healthcare provider's example hospitals. This underscores the need to improve health care services by reducing the costs for diagnosis and treatment while considering the marginalized population. Our results are in line with findings from studies in Tanzania that documented patients consulting traditional healers due to

financial constraints before reaching other healthcare facilities (Hinderaker et al., 2011a; Verhagen et al., 2010).

We observed a higher risk of delay among those who prioritized substance use, such as smoking and alcohol, as a cause of TB. These patients may have attributed their TB symptoms to coughing as a result of smoking and alcohol consumption and therefore delayed seeking help in proper heath care facilities. Educating patients on the risk factors for TB could potentially decrease patient as well as diagnostic delay while seeking health care.

LDFU in our study was massive. 44% of the respondents did not show up in the diagnostic centre after referral from the pharmacies and every third patient who did reach the centre, did not complete all required visits. Dropouts at the TB clinic did not differ from patients who did not attend any visit at the clinic at all. Although we could not trace whether these patients had completed TB treatment in other areas, we believe this to be partly the case as supported by other studies which documented tendencies of TB patients to continue with TB treatment elsewhere (Babu et al., 2008; Buu et al., 2003b; Rao et al., 2009).

The odds of LDFU among women were higher than those of males. Absence of financial autonomy made women miss diagnostic follow-up in healthcare facilities as indicated in the narratives. Furthermore women might have simultaneously used traditional methods and medical services instead of directly visiting healthcare facilities for proper diagnosis and treatment (Eastwood and Hill, 2004b). The association between female sex and LDFU in our study is contrary to other studies on adherence and loss to follow-up that found men to be more likely to be lost to follow-up (Gopi et al., 2005b; E. Johansson et al., 1999).

The category of perceived causes “other conditions”, such as prior illness and heredity, showed a marginally significant positive association with LDFU. Although

this finding was not well supported by the narratives, possible explanations for such results might be that patients with prior illness and who were previously treated for TB might have had unpleasant memories (Munro Salla, Lewin Simon, Smith Hellen, Engel Mark, Freitheim Atle, 2007) and did not want to make the same experiences again. This finding highlights the need for educating patients with regards to the importance of adherence and treatment completion so as to reduce loss to follow-up during treatment.

We found that dust exposures followed by sorcery were considered to be the main causes of TB symptoms in LDFU and non-LDFU. Alcohol and smoking were acknowledged as causes of TB after probing. Since ideas and perceptions about TB influence health-seeking behavior, the mentioned perceived causes influenced delay and diagnostic loss to follow-up. Clearly, this highlights the need for clarification on the perceived causes in the community that might help in shortening delay and LDFU and influencing the right help-seeking behaviour.

Findings from the narratives indicate that respondents often started seeking healthcare after coughing up blood (hemoptysis). Additionally, the absence of blood in sputum was interpreted as a ‘normal’ cough which would not be associated with TB. This suggests that there was a tendency among presumptive and TB patients to minimize the importance of their health conditions and discount the need for further treatment until they experienced some specific symptoms like hemoptysis, subsequently leading to patient delay and LDFU. Our findings are in line with findings from the study on health seeking behaviour among people with cough in Tanzania that showed patients with additional TB symptoms sought care earlier than those with no additional symptoms (Senkoro M, Hinderaker SG, Mfinanga SG, 2015).

Psychosocial distresses such as fear of being diagnosed with TB or HIV were recurring themes in the narratives. TB patients often experience considerable psychological and emotional distress as a result of their condition (Somma et al., 2008b; Weiss et al., 2006; World Health Organization, 2009), and presumptive TB patients anticipate the emotional burden of TB and of stigma eventually after being diagnosed with HIV that might lead to delay in seeking health care. Thus, this aspect requires some attention in case finding efforts.

Our study is the first to look at patient delay and loss to diagnostic follow-up among presumptive and confirmed TB patients within an intervention study in Tanzania. However, this study has some limitations. We included a small fraction of the presumptive and confirmed TB cases that participated in the big TB-PHARM intervention study to explore the factors associated with delay and LDFU in-depth. Due to the small sample, our analyses have provided few statistically significant results. However, the quantitative and qualitative findings of the study seemed to be coherent.

Furthermore, we relied on patient's recall of the duration of the delay in treatment seeking that might have introduced inaccuracy. However, our interviews were conducted with well-trained clinical workers who spent considerable time with the patients to obtain as accurate answers as possible. We attempted to limit inaccuracies by linking questions about delay with memorable events such as onset of symptoms until the first care seeking to a healthcare facility.

4.4.1 Conclusions

In conclusion, this study highlights that delay after the onset of symptoms and LDFU after referral from the pharmacies is substantial, especially for women. It also confirms the high proportion of patients consulting traditional practitioners and that this behavior is related to delay but not LDFU. This underscores the need for

interventions to ensure that more attention is paid to women's health needs for timely and sustained TB treatment and improved public awareness to reduce misperceptions of the cause and value for medical treatment. These findings also highlight the need to train and educate traditional healers on TB symptoms so they refer patients to the healthcare facilities for further treatment. The preference of the presumptive and confirmed TB patients to visit sub-optimal and unequipped healthcare facilities for treatment of TB-related symptoms as traditional healers may lead to diagnostic delay and LDFU as indicated in our study. These findings underscore the importance of strengthening the health sector to ensure that these patients are traced and linked to the healthcare facilities assuring early detection and effective treatment.

Supporting Information

Supplementary Table 4. Univariate analysis of factors associated with patient delay for presumptive and TB patients, n=136

Variable	OR	95% CI	P-value
Socio-demographics			
Sex			0.03
Male	1 (Ref)		
Female	2.21	1.07-4.54	
Age groups			
18-27	1 (Ref)		
28-37	0.72	0.29-1.77	0.48
≥38	0.88	0.34-2.28	0.80
Level of education			0.22
No formal education	1 (Ref)		
Primary/secondary	0.48	0.14-1.55	
Monthly household income			
Low income	1 (Ref)		
Middle income	2.18	0.92-5.17	0.07
High income	1.28	0.53-3.04	0.57
Perceived causes			
Ingestion	0.75	0.53-1.07	0.12
Magico-religious	1.15	0.84-1.56	0.35
Environmental causes	0.94	0.76-1.17	0.61
Substance Use	1.21	0.90-1.65	0.20
Person to person contact	0.97	0.71-1.34	0.89
Other conditions	1.0	0.73-1.35	1.0
Help-seeking			
Traditional healers	2.46	1.10-5.50	0.02
Religious healer	1.27	0.62-2.59	0.50
Hospital	0.85	0.42-1.74	0.67
Home remedies	1.28	0.52-3.12	0.58
Dispensaries	1.09	0.52-2.27	0.81

OR, Odds ratio; 95% CI= 95% Confidence Interval.

Supplementary Table 5. Univariate analysis of factors associated with LDFU for presumptive and TB patients, n=136

Variable	OR	95% CI	P-value
Socio-demographics			
Sex			
Male	1 (Ref)		
Female	3.51	1.70-7.23)	0.001
Age groups			
18-27	1 (Ref)		
28-37	1.07	0.46-2.51	0.86
≥38	1.62	0.65-4.05	0.29
Level of education			
No formal education	1 (Ref)		
Primary/secondary	0.68	0.23-1.93	0.47
Monthly household income			
Low income	1 (Ref)		
Middle income	1.24	0.54-2.86	0.60
High income	0.58	0.24-1.37	0.2
Perceived causes			
Ingestion	0.68	0.47, 0.98	0.04
Magico-religious	1.26	0.93-1.72	0.12
Environmental causes	0.92	0.75-1.14	0.49
Substance use	1.08	0.82-1.43	0.12
Person to person contact	1.09	0.80-1.50	0.56
Other conditions	1.15	0.84-1.56	0.36
Help-seeking			
Traditional healers	1.74	0.79-3.84	0.16
Religious healer	0.55	0.27-1.11	0.09
Hospitals	0.48	0.24-0.98	0.04
Home remedies	1.71	0.71-4.09	0.22
Dispensaries	0.64	0.31-1.30	0.21

OR, Odds ratio; 95% CI= 95% Confidence Interval

5. Traditional medicine practitioners and tuberculosis in Tanzania: What is their role?[3]

Grace Mhalu [1, 2, 3*] Constanze Pfeiffer [2, 3], Lydie Nzaisaba[2, 3] Karen Maigetter [2] , Elisabeth Zemp [2, 3], Lukas Fenner [4], Sonja Merten [2, 3*],

[1] Ifakara Health Institute Dar es Salaam Tanzania [2] Swiss Tropical and Public Health Institute, Basel, Switzerland Basel, Switzerland [3] University of Basel, Switzerland Basel, Switzerland [4] Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland

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Abstract

Background: Traditional medicine practitioners (TPs) are significant health care resources outside of the formal health services. They are widely used in Tanzania. However, the documentation of their understanding and practices towards tuberculosis (TB) management is limited. We explore the role of TPs in the management of cough and TB related symptoms in Tanzania.

Methods: In-depth interviews were used to investigate knowledge about TB and TPs practices related to the management of cough and TB related symptoms. We collected qualitative data from 30 TPs in three districts of urban, peri-urban and rural Tanzania. Open coding was used for labelling concepts, defining and developing categories based on participant's descriptions. We analysed data focusing on emerging themes, patterns, similarities and differences in the 3 districts.

Results: The age of TPs (19 males, 11 females) ranged from 30 to 65 years. More than half of the respondents knew how TB is transmitted. Diagnosis of cough and TB related symptoms were reported to be based on divinations, laboratory tests obtained from the hospital and patient-reported symptoms. Traditional medicines indicated as TB treatment included herbs, casting spells, and charms. Some practitioners in urban site reported that TB can only be treated in hospital whereas respondents from peri-urban and rural sites found that TB can be treated in hospitals as well as with traditional medicines. Only a few practitioners in urban, and peri-urban, but half of those in rural setting mentioned treating TB. Almost all TPs referred patients to the hospital for further treatment but there indicated minimal collaboration among the practitioners and the government or other stakeholders.

Conclusion: Results underline the need to educate TPs on TB symptoms, causes and treatment. Our observations may guide future public health interventions on the inclusion and collaboration with TPs for better TB case finding and management.

5.1 Introduction

Tuberculosis (TB) is the ninth leading cause of death worldwide, and a leading cause from infectious disease ranking above HIV/AIDS with 1.7 million deaths and 10.4 million TB cases in 2016 (WHO, 2017). Despite a recent global and national upsurge in TB treatment success rates, the disease remains a substantial killer and cause of disease burden especially in sub-Saharan Africa countries (WHO, 2016). Additionally, TB ranks the top three cause of the global burden of disease (GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, 2018).

Traditional medicine practitioners (TPs) are significant health care resources outside the formal health services provided by the government or non-governmental organizations and outnumber by far modern health practitioners in sub-Saharan Africa (UNAIDS., 2002). Evidence suggests that more than one third of TB patients in sub-Saharan Africa seek help from TPs before approaching modern health care facilities leading to delay in seeking health care, increased morbidity and mortality (Barker et al., 2006; Hinderaker et al., 2011b; Eliud R. Wandwalo and Mørkve, 2000a). Moreover, TPs act as the first entry point for health care seeking for the majority of people after the onset of TB symptoms (Barker et al., 2006).

Tanzania remains among the 30 countries in the world with high TB burden with 295 new TB cases per every 100,000 population (Ministry of Health and Social Welfare, 2013a; WHO, 2016). TB case detection strategies rely on passive case finding based on patients presenting themselves in healthcare facilities for diagnosis and treatment (Ministry of health and social welfare, 2006b; Ngadaya et al., 2008b). With such an approach, detection of TB cases is suboptimal due to complex pathways to care which often starts at TPs and not at formal health care facilities (Mfinanga and Mutayoba, 2008b; Mhimbira et al., 2016). Furthermore, a majority of people rely even primarily on traditional medicines for their primary health care requirements

(Brouwer et al., 1998).

Traditional healing practice is historically among the widely used and extensively accepted practices in Tanzania (Mbwambo et al., 2007), however, the documentation of its application in relation to TB control and management is inadequate. To our knowledge, no qualitative study on the role of TPs in TB control and management has previously been done in Tanzania. Up to now, interventions on intensified TB case findings have largely focused on biomedical rather than socio-cultural factors (Das and Horton, 2015). TPs knowledge and views have not been investigated and their practices are not well documented. (Das and Horton, 2015). We explored the role of TPs at an urban, semi-urban and rural site of Tanzania (Temeke, Bagamoyo and Ifakara districts) in the management of upper respiratory infection and TB related symptoms to determine if they could play a role in TB case finding and management.

5.2 Methods

Study settings

The study was conducted at the following three sites in Tanzania:

Urban site (Temeke district, Dar es Salaam Tanzania)

Temeke district of Dar es Salaam has a dense population of 1,369,000 people (The United Republic of Tanzania, 2013b). The main source of cash income is derived from the sale of food crops and from business (The United Republic of Tanzania, 2014b). The majority of the population are Christians and Muslims. The district is characterized by a small number of health care facilities compared to the other two districts (Kinondoni and Ilala). It has 135 health care facilities with only six private and public hospitals. The doctor population ratio in the district is estimated to be 1:4,074 (The United Republic of Tanzania, 2014b). In 2016, a total number of 4,495 TB cases (all forms) were identified in this district, of which 1,760 (43%) were smear-positive (Ministry of Health and Social Welfare, 2016a).

Peri-urban site (Bagamoyo district, Pwani Tanzania)

The peri-urban site of Bagamoyo is among the 6 districts of the Pwani region of Tanzania. The district is located at the coast, approximately 70km away from the commercial capital of Dar es Salaam, and has a population of 311,740 with only 136,506 individuals in formal employment. The main source of income in the region is farming (57.8%) and fishing (1.9%) (Tanzania National Bureau of Statistics, 2016c). The district is characterized by a low number of healthcare facilities and the doctor to population ratio is estimated to be 1:2051 (Tanzania National Bureau of Statistics, 2016c). The majority of the population are Muslims. Bagamoyo district is characterized by least number of healthcare facilities and has less than 5% TB notification rates per year (Tanzania National Bureau of Statistics, 2016a).

Rural site (Ifaka district Morogoro Tanzania)

The rural site of Ifaka is located in the Kilombero district in Morogoro region with a population of about 407,000 (The United Republic of Tanzania, 2013b). Farming is the main source of income (Tanzania National Bureau of Statistics, 2016d). The district is characterized by few public and private health care facilities (Ministry of Health and Social Welfare, 2014b). The district has a single refferral hospital which is the largest healthcare facility in Kilombero district. The population is a mixture of Muslims and Christians (Tanzania National Bureau of Statistics, 2016b). The doctor population ratio in Morogoro region is 1:19,475 (United Nations, 2014).The case notification rate is about 5.4% in the region with 3194 notified cases in 2016 (Ministry of Health and Social Welfare, 2016a).

Study population and sampling technique

We included TPs with more than eighteen years of experience in traditional healing practice who reported treating upper respiratory tract infection (i.e.' normal cough' as indicated by practitioners) and TB related symptoms (coughing for more than two weeks, night sweats, fever, and haemoptysis (coughing up blood). The study population consisted of 10 TPs at each study site.

Respondents were selected by purposive sampling with the help of the TB clinic at the Temeke referral hospital in Dar es Salaam, the Bagamoyo district hospital, and St. Francis hospital in Ifakara. The sampling procedure was considered the most effective approach for the identification and selection of information-rich cases, i.e. respondents knowledgeable and experienced in the management and treatment of cough and TB related symptoms (Creswell, 2014; Palinkas L et al., 2013; Patton, 1990).

As we were aware that most likely there were other key informants unknown to us, we further used snowball sampling (Biernacki and Waldorf, 1981; Browne, 2005) to

recruit further suitable participants. Residents and people around the study sites were asked about local TPs within their residence areas (Gessler et al., 1995c). They helped with recruitment from among their acquaintances until the required sample size was reached.

Study design

Qualitative in-depth interviews were used to investigate socio-cultural ideas and knowledge of TB in general, TPs approaches towards the management of coughs and TB related symptoms, and traditional medicines used by TPs for treatment of cough and TB related symptoms (Getachew et al., 2016).

Data collection

An interview guide was designed and, according to the accepted standards, pilot tested prior to data collection and modified where appropriate. The interview guide was developed in English and translated into the local language, Swahili. An interviewer with extensive training in qualitative research and in-depth interviews conducted the interviews in the local language. The interviews lasted 30 - 60 minutes and were audio-recorded. Data were collected from August 2016 to March 2017.

Data analysis

Data were transcribed verbatim. The transcribed data from voice recordings were read and re-read to gain an initial impression of the data and an in-depth understanding of participants' descriptions. All analyses were performed using MAXQDA version 12 (Verbi Software, Berlin, Germany).

We used open coding to labelling concepts, defining and developing categories based on properties and dimensions of participant’s descriptions (Strauss A, 1998). Subsequently, codes were grouped into categories and an inductive approach (ideas

emanating from the data itself) as well as a deductive approach (theoretical understanding, literature review and researcher`s experience) was used for data analysis. Two independent people checked for inter-coder reliability in order to improve coding instructions and individual codes (Kirilenko and Stepchenkova, 2016). The two individuals independently created codes and read randomly selected transcripts, one from each study site. They subsequently discussed the codes and resolved any disagreement arising from the codes.

Data were analysed focusing on emerging themes, patterns, similarities and differences. The framework analysis method of Gale,(Gale KN, Heath G, Cameron E, Rashid S, 2013b) developed for the analysis of qualitative data in multi-disciplinary research, was used for data analysis. The method was helpful in summarizing and reducing the data to answers the research questions.

5. 3 Results

Demographic characteristics

The demographic details of the study population are summarized in Table 13. Overall, we interviewed 30 TPs in three study settings. The age distribution of the practitioners ranged from 30 to 65 years with the exception of one practitioner being aged 75 years. There were 8 males (80%) at urban site, 7 (70%) per-urban and 4 (40%) in the rural site. Ninety percent of the practitioners were Muslims compared to ten percent Christians and other religions. Half of the respondents in urban and peri-urban were full-time TPs, half part-time TPs, combining TP with other occupations like farming and business. Almost all in rural site were part-time practitioners, combining TP and farming. The respondents reported a work experience as TP ranging from a minimum of five years to a maximum of 32 years. A long work experience (30 years and above) was reported by TPs particularly in the urban. As to the level of education, more than half of all TPs had a primary education, none had a university degrees or a vocational training education. In rural site, half of the interviewed TPs had no formal education. Furthermore, none of the TPs had been trained as community health care workers.

Table 13. Demographic characteristics of the interviewed Traditional practitioners

Characteristics	Urban n (%)	Peri-urban n (%)	Rural n (%)
Total	10	10	10
Sex			
Males	8 (80%)	7 (70%)	4 (40%)
Females	2(20%)	3 (30%)	6 (60%)
Level of education			
Primary	7 /70%)	60 (60%)	50 (50%)
Secondary	3 (30%)	1 (10%)	-
No formal education	-	3 (30%)	50 (50%)
Age			
30 years and above	10 (100%)	8 (80%)	9 (90%)
Below 30 years	-	2 (20%)	1 (10%)
Religion			
Muslims	9 (90%)	10 (100%)	8 (80%)
Christians or other religion	1 (10%)	none	2 (20%)
Work Experience as TP			
Range (years)	5-32 years	1-26 years	2-20
Five years or less	1 (10%)	3 (30%)	1 (10%)
Six years or more	9 (90%)	7 (70%)	9 (90%)
Occupation			
Full-time TH	5 (50%)	5 (50%)	2 (20%)
Part-time TH	5 (50%)	5 (50%)	8 (80%)

Mode of acquisition of the traditional healing practices

The mode of acquisition of the traditional healing practices described by the practitioners falls into six major routes as displayed in Table 14. These included, ancestor spirits subsequent to an experienced sickness, initiation of ancestral spirits, training through apprenticeship/religious institutions, inheritance from a family member subsequent to a sickness, own decision. All reported passing through a combination of routes.

> "I experienced unknown illness that made me collapse and lose consciousness for even four hours. I lost my work because of the condition. I had to come back home. My family members took me to a TP who said the ancestral spirits instructed that I have to inherit the job from my grandfather. I am a TP since then." *(male, Ifakara).*

> "I inherited this work from my father after he died. *(female, Temeke.)*

> "I liked traditional practices since I was young. I decided to go to a religious institution to get some training and later I stayed with a TP for a year for further training*." (male, Bagamoyo).*

> "The ancestral spirits wanted me to do this job. I first refused the spirits became furious with my decision. I eventually accepted the job and since then I have treated so many patients" *(male, Ifakara).*

> "I stayed with a TP for three months helping her and also to train for the job. I started practising at my home town afterwards." *(female, Temeke).*

In the urban site, most reported inheriting the practice from a family member (7 out of 10), contrasting to rural and peri-urban sites, where the majority stated to have become a healer initiated by ancestor spirits upon recovery from a sickness. Few practitioners in urban and peri-urban reported acquiring the practice through training

(apprenticeship/religious institutions), whereas none reported this in rural site. Only 2 stated to have become TPs by their own decision.

Table 14. Modes of acquisition of the traditional healing practice (multiple answers possible)

Mode of acquisition	Urban	Peri-urban	Rural
Ancestor spirits subsequent to an experienced sickness	5 (50%)	6 (60%)	8 (80%)
Inheritance from a family member	7 (70%)	4 (40%)	4 (40%)
Initiation by ancestral spirits	1 (1%)	4 (40%)	5 (50%)
Training through Apprenticeship/ religious institutions	3 (30%)	3 (30%)	1 (10%)
Inheritance from a family member subsequent to sickness	1 (1%)	2 (2%)	3 (30%)
Own decision	1 (1%)	1 (10%)	-

Health problems frequently treated

The interviewed TPs treated a number of health problems. Apart from different coughs and TB, these included: epilepsy, seizures, infertility, stomach diseases, witchcraft, fever, mental disorders, diabetes, pneumonia, malaria as well as different types of cancer. Treatment for health problems did not differ much among the TPs from the three study sites with the exception of cancer that was treated only by one TPs in the rural site. None explicitly reported treating HIV.

A male traditional healer from Bagamoyo stated:

> "I treat mental disorders, women infertility, sexually transmitted disease, different types of coughs and even TB."

> "I have successfully treated epilepsy, mental disorders, seizures and malaria to mention a few. All patients that I treated are in good health." *(female, Ifakara).*

TP knowledge on cough symptoms and TB

TPs in the three settings had limited knowledge on cough and TB related symptoms. They identified three distinct types of coughs. They referred to them as ‘normal cough’, ‘asthmatic cough’ and ‘TB cough’. Symptoms of a ‘normal cough’ were described as a dry cough without shortness of breath which lasted for some few days. Symptoms of ‘asthmatic cough’ included a productive cough that lasted for a longer period of time, and went along with fever as well as high body temperature.

‘TB cough’ was described by respondents as a productive cough accompanied by yellowish, thicker sputum. They also linked cough to TB in case of its co-occurrence with tiredness, difficulty in breathing, changes of skin and hair colour, and loss of consciousness. When asked about TB symptoms, only one TP in the urban setting could list more than half of the TB symptoms which include weight loss, haemoptysis, coughing for more than two weeks as well as fever. Some TPs, particularly in peri-urban, could not explain TB symptoms since they claimed not to have treated anyone with TB.

> "I have never treated anyone with TB therefore, I am not aware of what the symptoms are” *(female, Bagamoyo).*

> “I know three TB symptoms. The first one is coughing for a long time, second is tiredness and the last is changes in skin and hair colour.” *(male, Ifakara).*

Knowledge of TB causes and TB transmission

More than half of the respondents were able to describe that TB is transmitted through air from one person to another.

A female respondent in the urban setting said:

> “I know that TB is transmitted through air. If someone coughs without covering his mouth, he can transmit the disease” *(female: Temeke).*

Another TP in the rural reported that TB is transmitted through air or if an infected person eats or sleeps with those who are not infected:

> "I think TB is transmitted through air when someone coughs or even when you eat with someone who has TB; you can get the disease." (female: Ifakara).

The TPs could not differentiate the causes and risk factors for TB. There were different concepts with regard to the cause of TB among the TPs in the three sites. Half of the TPs in the urban site reported that TB is caused by dust, alcohol intake, cigarette smoking, and staying or working in crowded places such as buses and marketplaces. None of the TPs in the urban associated TB with witchcraft or evil spirits.

A male practitioner from the urban site explained it this way:

> "It is not true that TB is caused by either witchcraft or evil spirits. TB is caused by cigarette smoking and sometimes dust." *(male, Temeke).*

Contrasting to this, some TPs in peri-urban and rural settings believed TB was caused by witchcraft and evil spirits and two respondents from peri-urban and rural sites claimed that TB was caused by evil spirits.

> "Evil spirits can cause TB. It is another type of TB." *(female, Bagamoyo).*

Furthermore, only three TPs in the rural site said it was caused by bacteria. However, they could not mention the specific type of bacteria.

> "I know that TB is caused by a certain bacteria though I don't know the name of the bacteria." *(male, Ifakara)*

Other common causes mentioned in all sites were: a dirty environment, dust, drinking unboiled milk, inheritance and a combination of other diseases like asthma and HIV.

Knowledge of TB and HIV

We asked TPs if it is a must for a TB patient to have an HIV infection. TPs in rural site had a better knowledge of the relationship between TB and HIV than those in the urban and peri-urban. The majority in the rural site disagreed with this concept (8 out of 10):

> "It is not necessary for a TB patient to have HIV. Although these are co-infections, still I believe it's not necessary to have TB and HIV at the same time." *(male, Ifakara).*

In contrast, 5 out of 10 TPs in the urban and 4 out of 10 TPs in peri-urban agreed that a confirmed TB person must also have HIV.

Approaches to TB treatment

We observed an interesting pattern in the three study areas regarding TB treatment. In the urban, six out 10 TPs claimed that TB can only be treated in the hospital. None of the TPs thought to be able to treat and cure the disease, but only to relieve the symptoms.

A male respondent put it this way when asked:

> "None of us TPs can treat TB. We can only give herbs to alleviate TB symptoms. TB can only be cured in hospitals. There are some herbs that can treat a normal cough but not TB." *(male, Temeke).*

In the rural site 3 TPs mentioned that TB could be treated in hospitals but saw also a role for traditional medicine:

> "TB can be treated in the hospital but also with traditional medicines if hospital treatment fails. We sometimes receive patients who could not be cured with the treatment in hospitals. If I treat them with my herbs, they get completely cured." (*male, Ifakara*).

Likewise, 4 out of 10 TPs in peri-urban site claimed that traditional medicines can work if only the disease was caused by evil spirits.

> "TB can be treated by traditional medicine only if the disease was caused by evil spirits." *(male, Bagamoyo).*

Additionally, fear of being diagnosed with TB at the hospital was also mentioned as a reason for the patients seeking health care from a TP than in hospitals and other healthcare facilities.

> "Sometimes patients are afraid of being diagnosed with HIV at the hospital; that is why they visit us." (fe*male, Temeke).*

Traditional diagnosis of upper respiratory tract infections ('normal cough'), asthma and TB

Three different diagnostic procedures were described to be used by the TPs, include divinations (inquiring from the spirits and supernatural powers), laboratory test results from the hospital, and symptoms mentioned by the patients. The diagnostic procedures were said to be used either as a single procedure or in a combination.

We found that TPs in rural site who claimed to use divination as a diagnostic procedure far outnumbered those in urban and peri-urban (6 out of 10).

> "I inquired from the spirits regarding the health problem of the patient. The spirits informed me that the patient has TB." *(female, Ifakara).*

> "When a patient comes for treatment, I usually consult my spirits regarding the patient's problem. Immediately I know what the health problem is. If it is not witchcraft, I instruct the patient to visit the hospital." *(male, Ifakara).*

Only one TP in urban and one TP in peri-urban claimed to use divination as means of diagnosis for cough and TB related symptoms.

Diagnosis based on patient's symptoms was more common in urban and peri-urban settings. The TPs said they usually ask the patient first before they decide whether it was normal cough, asthma or TB.

> "I asked the patient regarding her symptoms before I could decide how to treat her. This is how I diagnose the different kinds of coughs." *(male, Temeke).*

> "I let the patient explain his problems and I listen carefully. Afterwards, I may advice the patient based on his explanations on whether to visit the hospital or to use traditional medicines. I don't use divinations or spirits for diagnosis of cough problems." *(female, Temeke).*

Diagnosis by hospital reports was frequently used by the TPs in urban and peri-urban sites. The patient is asked for the laboratory results before treatment.

> "I rely on laboratory results obtained from the hospital. I ask the patient to first get checked in a hospital. Afterwards, I can decide on how best to treat the patient." *(male, Temeke).*

> "Most of my patients visit hospitals first before coming here. This gives me a clear direction on how to treat them based on the diagnosis made at the hospital. "*(female, Bagamoyo).*

Treatment of coughs and TB related symptoms

Treatment approaches of a cough and TB were similar among the three study sites. All TPs reported using different traditional medicines for the treatment of either cough or TB related symptoms. These included: herbs (plant roots and leaves) that were either in powdered or liquid forms. Other traditional medicines included: honey, vinegar, lemons, garlic as well as ginger. Moreover, spells and charms, as well as spirits and divination were mentioned as part of treatment.

Variations in the views on treatment of TB were apparent in the three study sites. When asked if they could treat TB, only 2 TPs in urban and 3 TPs in peri-urban

agreed that they could do so TPs in the urban and peri-urban sites said that for TB patients, they only give some traditional medicines that can be used for a shorter time in order to alleviate pain before making referrals to hospitals for further treatment.

> "Once I suspect that I cannot treat the cough, I usually give the patients some herbs to relieve pain before I refer the patient to the hospital. If you send the patient away without any treatment, he might feel that you don't care. In addition, it's considered unethical in THs practices". *(male, Temeke).*

On the other hand, half of the respondents in the rural site said they treat TB and that they had previously treated TB patients with successful treatment outcomes.

> "I have never treated a TB patient before; however. I have some traditional medicines that can treat TB once I get a patient." *(Ifakara, female).*

Number and gender of treated patients

The number of patients treated did not differ in the three study sites. On average, TPs reported treating two to five patients daily with coughs and TB related symptoms.

TPs in the urban site reported treating more females than males. Only two respondents reported otherwise. When asked about underlying reasons, a male respondent said:

> "I treat more females than males. Females are weaker compared to males and encounter more health problems than males. The biological and physical make-up of a female makes her more vulnerable to health problems than a male." *(male, Temeke).*

Similarly, 6 out of 10 TPs in peri-urban reported treating more females than males; however, their given explanations differed from those in urban site

> “Females believe more in witchcraft than males. Whenever women encounter health problems, they think they are bewitched. This is the reason why females visit TPs more than males. It also might be because of a lack of financial resources, as TPs are cheaper compared to healthcare provided in hospitals.” *(female, Bagamoyo).*

In contrast, almost all TPs in the rural site (7 out of 10) reported treating both females and males.

Patient's admission to the treatment rooms

While none of the TPs in urban and only one in peri-urban reported admitting patients during treatment, in the rural site, half of the respondents reported to do so. Different reasons were given for this. In the rural site, TPs mentioned distance and the patient's condition as the reasons for admitting patients. Patients who lived far from the TPs and who were weak due to illness were admitted more often compared to others. However, patients with TB and other health conditions (e.g. fever, stomach problems) are admitted to a single room according to their gender.

> "I admit patients who come from far and those that are physically weak. I have separate rooms for males and females. Patients sleep together regardless of their health problems*." (female, Ifakara).*

Referrals to the hospital

We found that almost all TPs in the 3 study sites reported referring patients for further treatment if they could not provide treatment or if their treatment did not help. However, the majority of the respondents claimed to have changed their medication before the referrals were made. Three respondents, one from each study site, reported to refer patients to another TP if they could not provide treatment.

> "I change the medication before I refer the patient to another TP once I receive feedback that the treatment did not work. If traditional medicines from the other TP fail, then we can refer the patient to the hospital for further treatment." *(male, Bagamoyo).*

TPs were asked how long it takes them before referring patients for further treatment. While those in urban and peri-urban settings indicated a minimum of 3 days and a maximum of 7 days, TPs in the rural setting took a minimum of 3 days and a maximum of 2 weeks to refer patients for further treatment.

> “I prescribe traditional medicines for seven days. If the condition does not improve and the patient is getting worse, I immediately refer the patient to the hospital for further treatment.” *(male, Temeke).*

Costs of treatment

Three different explanations were provided by the TPs with regard to why they charge their patients. One reason for charging patients was that the payment received was used for obtaining an official treatment licence from the government. Others received payment to cover admission costs, while others used the payment to cover travel expenses to other regions to collect the traditional medicines.

TPs in all study settings commonly admitted that charging patients was not the main interest of their work but rather observing a positive treatment outcome for a patient. All TPs mentioned patient satisfaction with the provided treatment before asking for a payment.

> “Asking for a reimbursement from a patient is not the foremost priority. The patient has to get well first before I can ask for payments. Some of the patients are financially incapable of paying for their treatment. I treat even such patients.
>
> It’s very unfair to reject a patient because he cannot pay. Gods are not pleased with such behaviour” *(male, Temeke).*

Furthermore, costs of treatment varied significantly among the study settings. In urban site, the minimum costs ranged from ten thousand Tanzania shillings to a maximum of seventy thousand Tanzania shillings (4.5 USD to 32 USD). In peri-urban site from a minimum of two thousand to a maximum of fifty thousand (1 USD to 23 USD) and in the rural site from a minimum cost of two hundred shillings to a maximum of fifty-five thousand Tanzania shillings (0.08 USD to 25 USD). The amount of treatment costs depended on the type of treatment. In addition, more than

half of the TPs in the rural site accepted payment in kind (i.e sugar, rice and maize) compared to only three in peri-urban and none in the urban.

> "I accept all kinds of payments. If the patient does not have cash, he can bring something else e.g. rice or sugar. For others who cannot afford payment in cash, I receive even payment in kind." *(female, Bagamoyo).*

Costs for treatment were lower than those charged by hospitals and other healthcare facilities. The minimum payment could range from six thousand to a maximum of twenty five thousands Tanzania shillings for TB diagnosis for a single visit.

Collaboration with the government and other stakeholders

When asked about any collaboration with the government, only 3 TPs in the urban, 2 in rural and none in peri-urban said they would collaborate. Those who do collaborate in the urban reported to attend different seminars on TB events organized by the ministry of health in collaboration with other stakeholders. A TP in the rural reported to attend a seminar on TB to attend seminars organized by the government on other diseases such as HIV/AIDS but not TB.

5.4 Discussion

Findings from this study provide an insight into the current role of TPs in managing cough and TB related symptoms. Knowledge about cough and TB related symptoms were limited and varied across settings. Dust, witchcraft, smoking, alcohol abuse and living or working in crowded places e.g. in buses and in marketplaces were seen as causes of TB. TPs in the urban and rural sites had a mixed knowledge about how TB is transmitted and some in peri-urban could not respond to this question at all. Diagnosis for cough and TB related symptoms based on divinations (inquiring from the spirits and supernatural powers), laboratory test results from the hospital, and symptoms mentioned by the patients. The majority of the TPs accepted that effective TB treatment could only be obtained in hospitals. TPs in all study sites referred patients to the hospital for further treatment. Treatment costs 'normal cough' asthma and TB related symptoms ranged from a minimum of 200 to a maximum of 50 thousand Tanzania shillings (to 24USD).

We found that TPs reported treating a vast majority of diseases with traditional medicines and divinations as documented elsewhere (Gessler et al., 1995b). This finding highlights that TPs are an influential group in the primary health care system and can undoubtedly contribute to the health of the community. This underscores a need to involve TPs in national healthcare systems through effective training so they can support disease control strategies in the community. Furthermore, on average, TPs reported treating two to five patients daily with coughs and TB related symptoms. This finding is alarming and requires some attention since it may increase TB transmission in the community.

In this study, almost all of the TPs could mention how TB was transmitted. However, the majority lacked the ability to identify presumptive TB cases. Only one TP could mention about half of the TB symptoms. This indicates a limited knowledge of TB

symptoms among the TPs, as similarly documented elsewhere (Brouwer et al., 1998). Consequently, this might intensify the TB transmission cycle in the community since the TPs will not be able to identify and immediately refer patients to hospitals for further treatment. Public health interventions should focus on educating this important group in the community particularly on TB symptoms in order to control further TB transmission in the community.

We found that a majority of the healers did not have a clear knowledge of the causes of TB. While those in the urban related TB to cigarette smoking and overcrowding, their counterparts in the peri-urban and rural sites had different views and related the disease to evil spirits. Only 3 TPs in the rural site mentioned bacteria as a cause of TB. Our results confirm observations made in other studies that have documented perceptions of TB causes. Knowledge is usually higher in urban settings compared to rural settings in TB patients and in the normal population (Haasnoot et al., 2010; E. R. Wandwalo and Mørkve, 2000). This finding should be carefully reflected upon as assumptions like TB is caused by evil spirits complicates the health-seeking behaviour and increases delay for patients who seek care from TPs.

Acknowledgement by some TPs that TB can be treated only in hospital underlines the importance of harnessing such information among these practitioners as beneficial for the patients. The TPs could be trained to become TB treatment supervisors, an approach accepted by many TB patients (Banerjee et al., 2004; Wilkinson et al., 1999). Subsequently, the approach could assist in reducing the rate of loss to treatment follow-up and pre-treatment follow-up, a substantial health problem in low-income countries particularly in Africa (MacPherson et al., 2014a).

Diagnosis of normal coughs and TB was based on divination, laboratory results from hospitals and symptoms, no diagnostic measures (such as microscopy or Xpert) were used by TPs. This approach may undermine TB control measures. Some TPs,

especially those from urban and peri-urban, indicated to rely on the diagnostics of hospitals, but the time that elapses until they refer their patients may be too long. This leads to delay in diagnosis and consequently in seeking health care treatment at the appropriate healthcare facilities. TPs should be properly educated on the importance of proper, early TB diagnosis at healthcare facilities with optimal diagnostic tests.

Moreover, other TPs practiced herbal treatment and few used charms and the casting of spells. Using herbs for treatment of various diseases has a long history in African indigenous culture (Cunningham, 1993). Some of the respondents reported using both western remedies and traditional remedies. Our findings are similar with findings from treatment of malaria and HIV in Tanzania where the TPs and the patients reported to use both western and traditional remedies (Gessler et al., 1995a; Moshabela et al., 2017).

Females were more frequent among the TPs patients than males. TPs gave as an explanation that women are weaker, more likely to believe in witchcraft and less able to afford the costs of treatment in health facilities. As documented elsewhere, the low cost associated with TPs treatment makes it easier for women to access their services in comparison to men (Eastwood and Hill, 2004a). Our findings are also consistent with those from another study documenting that females made use of TPs more than males (WHO, 2006).

Furthermore, half of the practitioners in the rural site reported admitting patients from a long distance and who were weak due to illness. These patients were also admitted in the same treatment rooms, regardless of their health conditions and disease. This finding is alarming and should be further examined since social proximity among people has been documented as a risk factor for TB (Lienhardt et al., 2003).

Costs for treatment varied in the three study settings. They were rather low and affordable for the majority of patients, and some TPs treated their patients for free. This might be one of the explanations why patients prefer to seek help at TPs rather than in other health care facilities e.g.in hospitals. Our findings are consistent with findings in Gambia whereby patients sought healthcare at TPs as they were not able to afford treatment costs at other healthcare facilities (Eastwood and Hill, 2004a). Public and private health facilities should explore ways to mitigate costs for seeking healthcare in the marginalized population so that this group can afford care at optimal healthcare facilities.

Our results indicate that there exists very minimal collaboration among the TPs with the government or other stakeholders. One exception is, at least for some TPs, that they rely on the diagnostics of health facilities. This finding highlights the need for strengthening the partnership between the government and the TPs in Tanzania. It might motivate the TPs not only to refer patients for further treatment, but also to be aware of TB in general. Additionally, TPs could sometimes act as supervisors for the TB patients if given a chance as documented elsewhere (Banerjee et al., 2004; Wilkinson et al., 1999).

To the best of our knowledge this study is the first one to examine the roles of TPs in the management of TB in Tanzania. It is also the first study to investigate and contrast the practices of TPs in urban, peri-urban and rural areas of Tanzania. Our study is not without limitations. TPs might have displayed social desirability towards the interviewer and provided answers that they thought were likely to be favoured by the interviewer. However, we had assured the respondents that there were no wrong or right answers and that all their response were highly acceptable and valuable.

5.4.1 Conclusion

Findings from this study highlight insights into the possible role of TPs in TB management. They confirm the limited knowledge of TB among TPs. Further, it points out the different treatment practices including the use of herbs, divinations and use of charms and spells. Although referrals to hospitals for further treatment are found to be a common practice among the TPs, they but occur with delays. Results from this study underline the need to educate TPs on TB symptoms, causes, timely diagnosis and appropriate treatment to enable them for their inclusion and collaboration for a better TB management.

6. Traditional healers and tuberculosis in Tanzania[4]

Grace Mhalu [1, 2 3] Jerry Hella[1, 2 3] Yeromin P. Mlacha[1 2 3] Chistian Schindler [2 3] Elizabeth Zemp [2 3] Lukas Fenner [4]

[1] Ifakara Health Institute, Dar es Salaam, Tanzania [2] Swiss Tropical and Public Health Institute, Basel, Switzerland [3] University of Basel, Switzerland [4] Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland

[4] Working paper

Abstract

Introduction: At least one third of the tuberculosis (TB) patients in sub-Saharan Africa visit traditional healers (THs) before visiting modern healthcare facilities for TB treatment. We explored the role of THs in TB management in urban, per-urban and rural settings of Tanzania.

Methods: We included 90 THs, 30 from each study site and collected data on knowledge of symptoms and causes of TB, costs for TB treatment and calculated distance in meters. Cost distributions were described by their medians and interquartile ranges.

Results: The median age was 41.4 years (interquartile range [IQR] 37.5-49.7) and 54 (60%) were men. 5 (17%). 50% of the healers in peri urban and rural sites had low knowledge on TB causes. 24 (80%) in the rural setting reported to use charms and spells for treatment of cough and TB related symptoms compared to 12 (40.0%) in the urban setting and 17 (56.7%) in peri-urban. Maximum median costs for TB treatment in urban site were USD 4.61 [IQR 2.30-6.91] similar to peri-urban and 6.91[2.30-11.53] in the rural site. 37% of the THs in the rural site admitted patients during treatment compared to 10% in the urban and 16% in peri-urban (p=0.03). 11 (36.7%) of the healers in peri-urban resided < 1000 meters from a hospital compared to 28 (93%) in urban site and the rural site 24 (80%). There was a significant association between collaboration with the government and referring patients to hospital for further treatment (p =0.01).

Conclusion: THs had limited knowledge on cough and TB related symptoms. Treatment practices differed among the healers and costs for treatment were lower compared to formal treatment. THs should be educated on the importance of early and timely TB diagnosis and the collaboration between the healers and the government should be improved for better TB control.

6. 1 Introduction

Despite recent global and national increase in tuberculosis (TB) treatment success rates the disease remains a substantial killer especially in Sub-Saharan Africa countries particularly where HIV prevalence is also high (WHO, 2018). In such settings TB accounts for almost 40% of adult deaths where as in half of these cases the disease remains undiagnosed until death (Gupta et al., 2015). These results might be attributed to health seeking behaviour and access to health care among TB patients (WHO, 2018, 2017). In addition, they might be attributed to visits to health care providers with sub-optimal or no diagnostic capacities e.g. traditional healers (THs) for the first consultations before reaching facilities with TB diagnostic capacities (Barker et al., 2006). Furthermore, access to health care facilities is sometimes difficult for the presumptive and TB patients due to several factors such as geographical accessibility, suitability of the health services and the financial constraints (Barker R. et al., 2002; Kasse et al., 2006). Such factors may lead to the utilization of the THs than other health care providers (Eastwood and Hill, 2004a).

Almost 80% of the people living in Africa rely on traditional healing system for their primary health care requirement in spite of introduction to western treatment (WHO, 2000). Evidence suggests that THs are significant health care resources outside the formal health care services, and far outnumbered modern health care providers particularly in sub-Saharan Africa (UNAIDS., 2002). Additionally, at least one third of the TB patients in these settings visit THs before visiting modern healthcare facilities (Banerjee et al., 2000; Barker et al., 2006).

Tanzania still remains among 30 countries with high TB burden with 295 TB cases per 100,000 population (Ministry of Health and Social Welfare, 2013a; WHO, 2017). TB case detection is mainly done by passive case findings, by patients with TB symptoms presenting themselves to the health care facilities for diagnosis and

treatment (Ministry of Health and Social Welfare, 2013b). With such approach, the pathway towards diagnosis and TB treatment involve more than one health care provider and visits to THs which can lead to delay in diagnosis for TB patients (Hinderaker et al., 2011b; Said et al., 2017; Eliud R. Wandwalo and Mørkve, 2000a).

Traditional healing practices have co-existed since the colonial age and the number of the THs outweigh that of the modern practitioners in Tanzania (UNAIDS., 2002). The practice is broadly used and widely accepted in the country (Mbwambo et al., 2007), however, the documentation of its application towards TB management is scarce. To better understand the role of THs in management and TB control, we explored the role of THs in TB management in urban, peri-urban and rural settings of Tanzania.

6.2 Methods

Study settings

The study was conducted in the following three study sites

i. Temeke district, Dar es Salaam Tanzania *(urban site)*

Temeke district has a dense population of at least 1.4 million people (The United Republic of Tanzania, 2013a). The site has the least health care facilities compared to other districts (Ilala and Kinondoni) with six hospitals, eight health centers and 121 dispensaries (The United Republic of Tanzania, 2014a). The doctor population ratio in the district is estimated to be 1:4,074 (The United Republic of Tanzania, 2014a). In 2016, 4,495 TB cases (all forms) were notified of which 20% were notified in private health care facilities (Ministry of Health and Social Welfare, 2016a).

ii. Bagamoyo district, Pwani Tanzania*. (peri-urban site)*

Bagamoyo is among the six districts in Pwani region approximately 70km away from the commercial capital of Dar es Salaam with a population of about 311,740 people (The United Republic of Tanzania, 2013a). The district is characterized by least number of healthcare facilities with one public hospital. The doctor population ratio is estimated to be 1:2051 (Tanzania National Bureau of Statistics, 2016a). The region has less than 5% TB notification rates whereas it notified a total of 2,271 cases (all forms) in 2016 (Ministry of Health and Social Welfare, 2016a).

iii. Ifaka district Morogoro Tanzania *(rural site)*

The rural site is located in the Kilombero district, Morogoro region, in South central Tanzania with a population of about 407,000 people (The United Republic of Tanzania, 2013a). The district is also characterized by few healthcare facilities and has a single referral hospital which is the largest healthcare facility in Kilombero district (Tanzania National Bureau of Statistics, 2016b). The case notification rate is

about 5.4% in the region with 3194 notified cases in 2016 (Ministry of Health and Social Welfare, 2016a).

Study population

THs with experience in traditional healing system were included in the study from August 2017 to January 2017 until the required sample size of 90 THs (30 THs in each study site) was reached (Figure 12). Inclusion criteria were, i) ≥18 years of age at recruitment ii) Treated upper respiratory tract infection (i.e normal cough as indicated by healers) and TB related symptoms (ie coughing for more than two weeks, haemoptysis, night sweats and fever) and, iii) reported to treat TB. THs were identified with the help of health care providers from the TB clinic in Temeke referral hospital Dar es Salaam, Bagamoyo district hospital in Bagamoyo and Chronic Disease Clinic of Ifakara (CDCI) in St Francis hospital Ifakara. We excluded healers who did not provide consent.

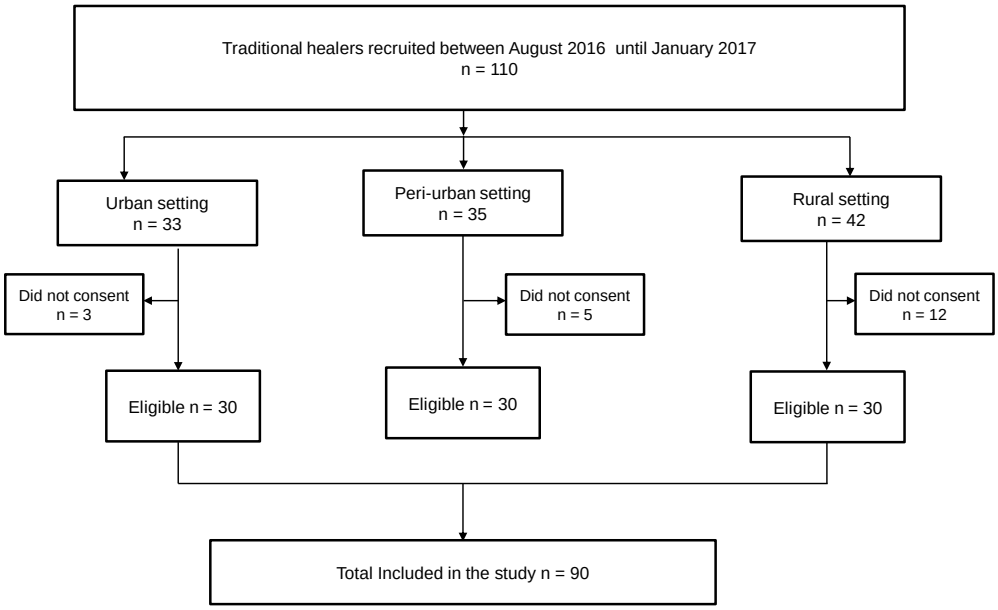

Figure 13. Flowchart of the study population. Participants were enrolled until the final target of 90 THs (30 healers in urban, peri-urban and rural site) was reached

Data collection and definitions

Interviews

THs were interviewed with a structured questionnaire and we collected data on socio-demographics, THs knowledge on cough and TB, as well as treatment of cough and TB related symptoms. The interviews were carried out with a research officer with extensive experience in conducting research. Data were recorded on tablets using the OpenDataKit (ODK) application (Steiner et al., 2016).

Geographical Information System (GIS) data

We collected geo-coordinates data using Android tablets (Samsung) from the three study sites. The data included THs households (working places) health care facilities as pharmacies, dispensaries, hospitals (public and private), and healthcare centres. The Tanzania region shape file was obtained from the Tanzania National Bureau of Statistics (NBS). We used ArcGIS version 10.5 (Esri; Redlands, USA) to produce the map.

Definitions

A TH was defined as a person who is recognized by the community in which he lives as competent to provide healthcare by the use of plants, animals or other mineral substances and other methods based on socio-cultural and religious backgrounds as well as knowledge, attitudes and beliefs that are predominant in his/her community (Kubukeli, 1999; WHO, 1977).

Traditional medicine was defined as the sum total of the knowledge, skill, and practices based on theories, beliefs, and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health as well as in the prevention, diagnosis, improvement or treatment of an illness (WHO, 1977; WHO traditional medicine strategy. 2014-2023, 2013).

Statistical analysis

We performed descriptive analyses to summarize the data and used Chi square test of association to assess differences between groups in categorical variables**.** We used the threshold of a p-value less than 0.05 for decision on statistical significance. We also computed medians and Interquartile ranges (IQR) on the costs for service provision as reported by the healers in the study sites. Furthermore, we used household ownership of items to generate wealth index, based on the existing literature (The United Republic of Tanzania, 2013a). Subsequently, we categorised the study participants into five quintiles of social economic status as documented in other settings (Kuwawenaruwa et al., 2015; Ministry of Health and Social Welfare, 2016b; Vyas and Kumaranayake, 2006). The first quintile presents THs with lower social economic status (poorest) while the second presents the poor, and the last quintile non-poor (the rich) THs. All statistical analyses were performed using Stata version 14.0 (Stata Corporation, College Station, TX, USA).

Assessment of knowledge on TB symptoms and TB causes

We combine knowledge questions on TB causes (i.e. bacteria, dust, witchcraft, prior illness, and unknown causes) and TB symptoms (i.e. cough, fever, night sweats) to form an index. Consequently, we used the index to categorise THs into three main categories (high, medium and low knowledge). The categories included THs with poor knowledge ranging from 0-3 score, medium knowledge from 4-6 score and high knowledge from 7-10 score. The index to asses knowledge were calculated based on other similar studies (Kigozi et al., 2017; Uiso et al., 2006).

Analysis of distance to the near healthcare facility

We calculated the Euclidean distances in meters as a linear distance between the TH's household (working place) and the nearest health care facility (pharmacy and hospitals) in all the three study sites. The nearest facility tool in Arch GIS was used to obtain the distance from the TH's household and the near healthcare facility. We then imported the results of the Euclidean distances into Stata software and calculate the average distance between the THs household and the near healthcare facility.

6.3 Results

Demographic characteristics

We analysed data of 90 THs, 30 participants in each study site. The median age was 41.4 years (interquartile range [IQR] 37.5-49.7) and 54 (60%) were men (Table 15). Older THs were found more in rural site comparing to urban and per-urban settings (median age 44.3 years, [IQR 35.5-51.8] vs 42.2 years [IQR 37.5-59.2] in urban and median age 38.7 years [IQR 33.4-44.7] in peri-urban. Overall, more than half of the respondents had primary level of education 60 (66.7%) and were Muslims 80 (88.9%). While most of the THs in rural were part time practitioners combining TP with farming 19 (63.3%), majority in urban and peri-urban practised full-time 18 (60.0%) and 17 (56.7) respectively. 27 (30.0%) of the THs heard about TB information from family members and friends. Overall, 57 (63.3%) of the practitioners treated two patients daily. 11 (45.8%) of the practitioners in peri-urban treated more than two patients daily while 9 (10.0%) of the healers in urban treated more than five patients daily.

Table 15. Demographic characteristics of the traditional healers

Variable	All n (%)	Urban n (%)	Peri-urban n (%)	Rural n (%)
Age in years median (IQR)	41.4 (35.5-49.7)	42. (37.5-59.2)	38.7 (33.444.7)	44.3 (35.5-51.8)
Age groups				
24-34	16 (17.8)	4 (13.3)	8 (26.7)	4 (13.3)
35-44	36 (40.0)	12 (40.0)	14 (46.7)	10 (33.3)
45-54	18 (20.0)	5 (16.7)	4 (13.3)	9 (30.0)
>55	20.0 (22.2)	9 (30.0)	4 (13.3)	7 (23.3)
Sex				
Females	36 (40.0)	11 (36.7)	7 (23.3)	18 (60.0)
Males	54 (60.0)	19 (63.3)	23 (76.7)	12 (40.0)
Level of education				
No education	21 (23.3)	4 (13.3)	8 (26.7)	9 (30.0)
Primary education	60 (66.7)	21 (70.0)	18 (60.0)	21 (70.0)
Secondary education	9 (10.0)	5 (16.7)	4 (13.3)	0
Religion				
Muslims	80 (88.9)	27 (90.0)	27 (90)	26 (86.7)
Christians	10 (11.1)	3 (10.0)	3 (10.0)	4 (13.3)
Household income				
≤300 USD per month	75 (83.3)	25 (83.3)	22 (73.3)	28 (93.3)
>300 USD per month	15 (16.7)	5 (16.7)	8 (26.7)	2 (93.3)
Occupation				
Full time	42 (46.6)	18 (60.0)	17 (56.7)	7 (23.3)
Partly businessman	22 (24.4)	9 (30.0)	9 (30.0)	4 (13.3)
Partly farmers	26 (28.9)	3 (10.0)	4 (13.3)	19 (63.3)
Wealth Quintile				
Poor –households	18 (20)	1 (5.6)	6 (33.3)	11 (61.1)
Second	18 (20)	2 (11.1)	3 (16.7)	13 (72.2)
Middle	18 (20)	4 (22.2)	8 (44.4)	6 (33.3)
Fourth	18 (20)	11 (61.1)	7 (38.9)	-
Non-poor households	18 (20)	12 (66.7)	6 (33.3)	-
Sources of TB information				
Health worker	21 (23.3)	9 (42.7)	6 (28.6)	6 (28.6)
Family member/friends	27 (30.0)	5 (18.5)	9 (33.3)	13 (48.1)
Radio/newspaper	13 (14.4)	4 (30.8)	5 (38.4)	4 (30.8)
School	15 (16.7)	8 (53.3)	4 (26.7)	3 (20.0)
Others (Gods, MDH)	14 (15.6)	4 (28.6)	6 (42.8)	4 (28.6)
Number of patients treated in days				
0-2	57 (63.3)	22 (38.6)	13 (22.8)	22 (38.6)
3-4	24 (26.7)	6 (25.0)	11 (45.8)	7 (29.2)
≥5	9 (10.0)	2 (22.2)	6 (66.7)	1 (11.1)

IQR, interquartile range, MDH Management development health, USD United States dollar equivalent to 2168 at the time of data collection

Knowledge on TB symptoms and TB causes.

Overall only 13 (1.4%) of the THs had high knowledge of TB symptoms (Table 16). The rural site had slightly high proportion of THs with high knowledge of TB symptoms 5 (17%) compared to those in urban and peri-urban. While more than half or the healers in the urban site had medium knowledge on TB symptoms 26 (86.7%), similarly to the healers in peri-urban 21(70.0), a low proportion of healers with medium knowledge was observed in the rural site 14 (46.7%). A high proportion of healers with low knowledge on TB symptoms were observed in the rural site 11 (37%).

Only 15 (16.7%) of the healers has high knowledge on the causes of TB. Half of the healers in peri-urban 15 (50%) and half in the rural site 15 (50%) had low knowledge on TB causes almost similar to the healers in the urban site 12 (40%).

Table 16. THs Knowledge on TB symptoms and causes

Variable	All n (%)	Urban n (%)	Peri-urban n (%)	Rural n (%)
Knowledge on TB symptoms				
High knowledge[1]	13 (14.4)	4 (13.3)	4 (13.3)	5 (16.7)
Medium knowledge[2]	61 (67.8)	26 (86.7)	21 (70.0)	14 (46.7)
Low knowledge[3]	16 (17.8)	-	5 (16.7)	11 (36.7)
Knowledge on TB causes				
High knowledge	15 (16.7)	6 (20.0)	5 (16.7)	4 (13.3)
Medium knowledge	33 (36.7)	12 (40.0)	10 (33.3)	11 (36.7)
Low knowledge	42 (46.7)	12 (40.0)	15 (50.0)	15 (50.0)

[1] High knowledge scores ranging from 7-10

[2] Medium knowledge scores ranging from 4-6

[3]Low knowledge score ranging from 0-3

Traditional management of cough and TB related symptoms

All THs used herbs to treat cough and TB related symptoms (Table 17). In the urban setting, 26 (86.7%) of the healers treated patients with substances (i.e. garlic, honey) compared to 23 (76.%) in peri-urban setting and 18 (60.0%) in the rural setting. More than half of the practitioners 24 (80%) in the rural setting reported to use charms and spells for treatment of cough and TB related symptoms compared to 12 (40.0%) in the urban setting and 17 (56.7%) in the rural setting. Other treatments (ie bathing patients, use of holy water were commonly mentioned in the peri-urban site 18 (60.0%) compared to those in urban and rural sites.

Table 17. Reported practice on treatment of TB and cough related symptoms

TB treatment and cough symptoms	All n (%)	Urban n (%)	Peri-urban n (%)	Rural n (%)
Herbs	90 (100)	30 (100)	30 (100)	30 (100)
Charms, spells and lying of hands	53 (58.9)	12 (40.0)	17 856.7)	24 (80.0)
Substances (garlic, ginger)	67 (74.4)	26 (86.7)	23 (76.7)	18 (60.0)
Others (bathing, holy water)	43 (47.8)	11 836.7)	18 (60.0)	14 (46.7)

Costs of treatment for cough and TB related symptoms.

Overall, the maximum median costs for treatment of cough or TB related symptoms was 4.61 [IQR 2.30-6.91] (Table 18). For the TH in the urban site, the maximum costs until the end of treatment were USD 4.61 [IQR 2.30-6.91] while the minimum were USD 0.92 [IQR 0.46-2.30]. Similarly, the maximum costs in peri-urban were 4.61 [IQR 2.30-6.91] and the minimum costs were USD 0.92 [IQR 0.46-2.30]. In the rural site, the maximum costs were 6.91[2.30-11.53] and the minimum costs stood at 1.38 [IQR 0.92-2.30]. For other diseases like malaria, pneumonia, and evil spirits, the maximum median costs of treatment were USD 13.37 [IQR 6.91-23.06] and the minimum costs were 2.30 0.9 [IQR 2-2.30].

Table 18. Costs (in USD) for treatment from THs perspective

Costs	All median (1QR)	Urban median (1QR)	Peri-urban median (1QR)	Rural median (1QR)
Maximum TB treatment[1]	4.61 (2.30-6.91)	4.61 (2.30-6.91)	4.61 (2.30-6.91)	6.91 (2.31-11.53)
Minimum TB treatment	0.92 (0.92-2.30	0.92 (0.46-2.30	0.92 (0.92-2.30	1.38 (0.92-2.30)
Maximum single consultation[2]	3.23 (2.30-4.61)	4.61 (4.61-6.91	3.22 (2.30-4.61)	2.30 (2.30-3.22)
Minimum single consultation	0.92 (0.46-2.30)	0.92 (0.46-1.84)	0.92 (0.46-2.30)	1.38 (0.46-2.30)
Maximum other diseases[3]	13.84 (6.91-23.06	15 .0 (9.23-23.06)	10.38 (6.91-18.45)	15.0 (6.92-23.06)
Minimum other diseases	2.30 (0.92-2.30)	2.30 (0.92-2.30)	2.30 (0.92-2.30)	2.30 (1.38-2.30)

IQR, interquartile range, USD, United States Dollar (1 USD=2168 Tanzania shillings, exchange rates as of August 2016)

[1] Costs for the entire TB treatment period

[2] Cost for a single consultation with the healer

[3] Costs for treatment of other diseases e.g., Malaria, diabetes

Admission and referral system

We found that 37% of the THs in the rural site admitted patients during treatment compared to 10% in the urban and 16% in peri-urban (p=0.03). For the referrals, 67 (74.4%) of the healers referred patients to either near hospital, a TB clinic or a dispensary for further treatment if they could not treat the patients. Moreover 31 (34.4%) of the healers reported referring patients to other healers. Out of these, 14 (46.7%) TH's from the rural site referred patients to other healers compared to those in urban and in peri-urban 8 (26.7%) and 9 (30.0%) respectively. The interval until referral to either formal healthcare facilities (e.g. hospital) or informal healthcare facility (i.e. other THs) was slightly different in the study sites. While half of the healers in the rural site took seven days or more to refer patients for further treatment, only 9 (30%) in urban site took seven days or more and 10 (33.3%) in the peri-urban reported referring patients in seven days or more (p=0.01).

Distance from the TH to a near health care facility

Figure 14 display the spatial distribution of the THs and the healthcare facilities. While the urban site is characterised by many healthcare facilities, in the peri-urban and rural site are characterised by few hospitals. In addition, the THs in the urban setting are sparsely distributed compared to peri-urban and rural sites. Generally, 70% of the healers lived more than 1000 meters from a referral hospital. The peri-urban setting had a lower proportion of healers who reside 1000 meters or more from a hospital 11 (36.7%) compared to the urban site where 28 (93%) of the healers lived more than 1000 meters from a nearby hospital and 24 (80%) in the rural site.

The overall median total distance from the TH's household to a near hospital was 2072.5 meters [IQR 1362.5-3627]. For the TH's in the urban setting, the median distance to the near hospital was 4602.4 meters [IQR 3227.1-5614.5] compared to 1231.2 meters [IQR 884.1-1650.3] in peri-urban and 2418.9 meters [IQR 1759.1-

3069.6] in the rural setting. Additionally, the total median distance to a nearby pharmacy was 868.5 meters [IQR 250.3-1566.4] in the three sites. In the urban setting, the median distance was 1425.2 meters [IQR 1132.7-1933.2] higher than that of the peri-urban site 235.5 meters [IQR 149.8-328.9] and somewhat low than that of the rural site 1353 meters [IQR 707.1-1687.9].

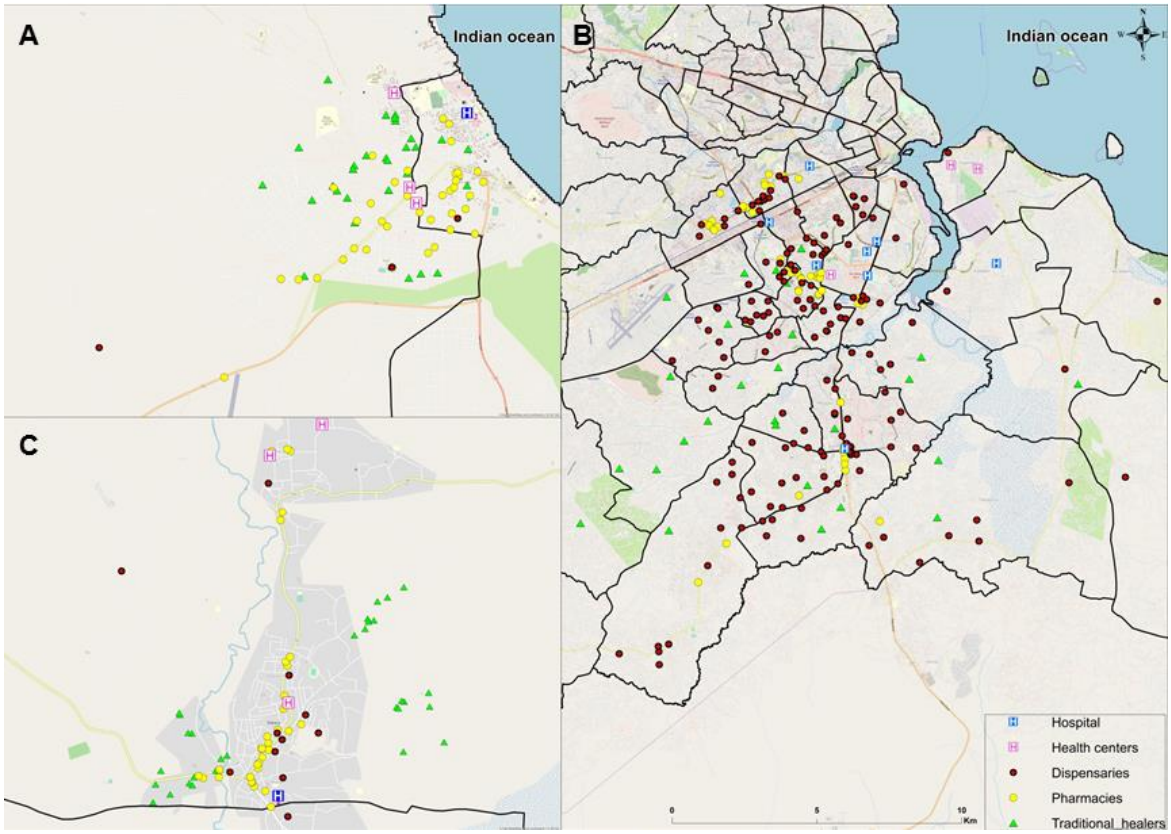

Figure 14. Geographical analyses of health care facilities in urban, peri-urban and rural sites. Panel A: Spatial distribution of healthcare facilities in the peri-urban site (Bagamoyo Pwani Tanzania). **Panel B:** Spatial distribution of healthcare facilities in the urban site site (Temeke, Dar es Salaam Tanzania). **Panel C:** Spatial distribution of healthcare facilities in the rural site urban site (Ifakara, Morogoro Tanzania**).**

Collaboration with the government and other stakeholders

Overall, only 16 (17.8%) had a collaboration with the formal health care providers in terms of referring patients and attending programmes prepared by the government or other stakeholders. The proportion of healers with high collaboration was from the urban setting 9 (30.0%). Healers from peri-urban and the rural site had the lowest level of collaboration with the government or any other stakeholders 4 (13.3%) and 3 (10.0%) respectively. We found a significant association between collaboration with the government and referring patients to either a hospital, TB clinic or dispensary for further treatment once the healer could not treat the patient (p =0.01).

6.4 Discussion

We report data from a short survey on the role of TH's in TB management and treatment in Tanzania. We found that sources of TB information among the healers were obtained more from the family members and friends. Majority of the healers treated two patients per day. The level of knowledge on TB symptoms and causes was limited among the healers. Furthermore, traditional management of TB was mainly through the use of herbs and the costs for TB treatment did not differ among the healers. All healers referred patients for further treatment. The distance between the healers household to a near healthcare facility was minimal. We found limited collaboration among the healers and the government and an association between having collaboration with the government and referring patients for further treatment.

We found that, knowledge on TB causes and symptoms of TB were particularly limited. The most notable gap on knowledge was found on causes of TB where some of the healers related TB with substances like dust and other causes like witchcraft. Some of these beliefs have a negative effect on the spread of TB not only to the healers but also to the patient and community at large. This finding highlights the need to educate and train the TH's on the symptoms and causes of TB. Educating the healers could significantly improve the health of entire community since they act as the first entry to the healthcare utilization for the majority of people in the community (Haasnoot et al., 2010).

Different approaches were used to manage and treat TB. Majority of the healers used herbs for the management of cough and TB related symptoms. Use of herbs for treatment of diseases has a long history. Herbs have proven to have both good outcomes and side effects not only for TB but also for Malaria in Tanzania (Gessler et al., 1995a). Our results are in line with some other studies that have documented the use of herbs and other substances in treatment of diseases which had led to

substantial health outcomes as increased mortality, morbidity and poor performance status among the patients (Barker et al., 2006). It is important that there should be clear regulations on the use of herbs for treatment so as to reduce poor health outcomes in the community (Mbwambo et al., 2007).

Costs of treatment were low compared to costs that patients incur at formal healthcare as documented in Tanzania and in Malawi (Gospodarevskaya et al., 2014; Kemp et al., 2007). We believe that this might be one of the reasons for most of the presumptive and TB patients to visit traditional healers instead of other healthcare facilities due to the financial burden associated with treatment in confirmed and presumptive TB patients as documented elsewhere (Eastwood and Hill, 2004a).

Distance from the healer's household to the a near health facility (pharmacies or hospital) was reported to be somehow short compared to other studies that have documented long distance from the patients household to a healthcare facility and that it is attributed to poor health outcomes and a risk factor for death (Barker R. et al., 2002; Kelly et al., 2016). Confirmed and presumptive patients often use TH's because of the long distance to the healthcare facilities (Eastwood and Hill, 2004a). However, in our study the median distance in meters from the THs household to a hospital or pharmacy was somewhat shorter implying that most of the healers lived near formal healthcare facilities. Therefore, we believe that the utilization of THs is not only attributed to distance but also to factors such as stigma, beliefs that TB can only be treated by THs, and perceptions that TH's treatment is short and effective (Edginton M. et al., 2002; Liefooghe et al., 1997; Miller et al., 2017).

We found that, there exists a minimal collaboration among the THs, the government and other stakeholders. This finding is crucial in TB case control as it highlights the finding substantiates the importance of including these important healthcare providers in the formal health care system. Such partnership may motivate the THs to act as DOT supervisors for the TB patients given a chance as it was found in India and South Africa (Banerjee et al., 2004; Wilkinson et al., 1999).

To our knowledge, this is the first survey to explore TB management among the healers in Tanzania. Furthermore, it is the first study to document the costs of treatment from the healer's perspective, calculate distance, and show the spatial distribution of the THs and the healthcare facilities in urban, peri-urban and rural Tanzania.

Our findings are not without limitations. We did not collect patient's data to compare the distance to the healers. We also included only a fraction of the TH's therefore our sample size was small. We might have missed some information from other healers because of our small sample size.

6.4. 1 Conclusion

THs had limited knowledge on cough and TB related symptoms. Treatment practices differed in the urban, peri-urban and the rural settings of Tanzania. Findings from this study highlight the association between collaboration among the healers, the government and other stakeholders. It further points out to lower costs associated with TB treatment. These observations may guide public health interventions for example of educating the THs on the importance of early and timely TB diagnosis. On the other hand, integration and collaboration between the healers and the formal health care providers should be improved especially in the peri-urban and rural settings.

7 General discussion

7.1 Summary of the key findings

The aim of this PhD project was to examine the community determinants of health care seeking in relation to the socio-cultural factors and gender in Tanzania. Specifically, the aim was: (i) to determine the pathways and costs of care among the confirmed and presumptive TB patients in Tanzania; (ii) to study LDFU before TB diagnosis and its determinants; and (iii) to study the roles of THs[5] in TB management comparing urban, peri-urban and rural districts of Tanzania. The results of these chapters are presented in details in chapter 3. The discussion and implications of these results are presented in the section hereafter.

7.1.1 Main Findings

Pathways to care in confirmed TB patients were complex compared to the presumptive patients. In confirmed patients, pathways involved several visits to health care facilities before TB diagnosis while that of the presumptive patients were more direct with only one or few visits to healthcare facilities before TB diagnosis. Confirmed and presumptive TB patients spent a median of 31% of their monthly household income on health expenditure for all five visits to healthcare facilities. Indirect costs were considerably higher than direct costs both in confirmed and presumptive TB patients.

Results obtained from the intervention study indicate a patient's delay of ≥3 weeks was in almost two thirds of the respondents and LDFU from the pharmacies to the TB clinic was observed in 44.1%. Prior consultations with THs were associated with patient delay but not LDFU. Gender differences were observed in patient delay and LDFU whereby the odds of patient delay were higher in females than in males, and LDFU was also higher more in females than in males.

[5] THs used throughout the general discussion to equally stand for THS or TPs

THs had limited knowledge on cough and TB related symptoms, and the knowledge varied across settings. Treatment for both cough and TB related symptoms was cheaper than that of the formal healthcare providers. Almost all practitioners referred patients to the hospital for further treatment. Collaboration among the THs, the government (NTLP) and other stakeholders was limited.

7.1.2 Pathways to care

It has been found that the pathways to care for both the presumptive and TB patients are not direct. They involve more than one healthcare provider with sub-optimal diagnostic equipment before TB diagnosis (Shete P.B et al., 2015; Veesa et al., 2018; Yellappa et al., 2017). We reconstructed pathways to care up to five visits from the onset of TB symptoms to TB diagnosis. The confirmed TB patients have shown to have more complex pathways and had more visits compared to the presumptive patients whose pathways were direct. To the best of our knowledge, this is the first study to consider pathways to care among the confirmed TB patients comparing them to the presumptive TB patients in an urban society of Tanzania.

Furthermore, from the analysis of the research question 1 it was observed that the confirmed TB patients (TB-DAR cohort) started healthcare seeking at the pharmacies while the presumptive patients started health care seeking at the hospitals. When investigating the healthcare seeking among the presumptive patients in our second research question on LDFU, seeking help from the pharmacies was considered the most important choice after the onset of symptoms. We could not substantiate why the confirmed TB patients from the TB-DAR cohort started their healthcare seeking from the pharmacies while the presumptive TB patients sought care first at the hospitals. On the other hand, we found in the analysis of the second research question (LDFU study) that presumptive patients started healthcare seeking at the pharmacies. However, it is clear that our results

indicate that the confirmed and presumptive TB patients usually consult more than one healthcare provider before TB diagnosis. In line with our results, a recent study from a prevalence survey in Tanzania showed that a majority of the presumptive TB patients had more than one visit to the healthcare facilities for their TB symptoms and some with sub-optimal TB diagnostics (Senkoro et al., 2015a).

Gender differences have also been documented to play a role in treatment seeking and pathways to care (Gosoniu et al., 2008a; Thorson et al., 2000a). When investigating the healthcare seeking and LDFU in relation to gender differences, we found that women were lost more during the diagnostic period compared to men and the association was statistically significant (chapter 3). Furthermore, both males and females sought care from the religious and THs similar to other studies (Eastwood and Hill, 2004a). Additionally, the preferences of seeking healthcare from the traditional and religious healers were associated with psychological comfort and financial autonomy notably among women. Women who do not have financial autonomy usually seek care later and with healthcare providers with sub-optimal diagnostic equipment (Chard, 2009). This has also been noted in our intervention study. Women had to depend on their husbands for financial resources before visiting the healthcare facilities.

Several factors that led to complicated pathways to care which eventually led to delay in health care seeking have been investigated including: stigma, financial hardships and female gender (Cai et al., 2015; Miller et al., 2017). Moreover, the spatial distributions of healthcare facilities and the distance from the patient household to the healthcare facilities have been documented to have an impact on healthcare utilization and treatment completion (Buor, 2003; Ibrahim et al., 2014).

Distances from the patient's household to the nearest healthcare facility was somehow shorter in our study than in the study of (Mfinanga and Mutayoba, 2008a),

and we did not find any association between distance and patient characteristics. Our results are contrary to some other results that found distance to have an impact on patient characteristics such as diagnostic delay (Sreeramareddy CT, Oin ZZ, Satyanarayana S, Subbaraman R, 2014).

As for the use of THs during the pathways to care, our results from objective one (TB-DAR cohort) and those of objective two (intervention study) documented a difference. While there was substantial use of THs in participants our intervention study (chapter 3), few visits were reported from participant of the cohort (chapter 4). Although we could not examine the spatial distribution of healthcare facilities and THs for the intervention study, in the cohort study we observed that most of the healers lived in the periphery while most of the healthcare facilities were situated mainly in the urban centers. This might be among the reasons as to why the patients in the cohort visited THs less than those in the intervention study. In chapter 6, when we investigated the distance from the THs to the nearest health care facility, we found that the distance was shorter from the THs household to either a TB clinic or a hospital. This finding could partly explain the preferences of using traditional health practitioners are not only due to longer distances from the patients' household to a nearby healthcare facility or a lack of financial resources to afford treatment in other healthcare facilities. As it was observed in our study, this also can be attributed to an individual's own preference to either visit the hospital or a TH. It may be attributed to perceptions that traditional treatment may be shorter and effective compared to the hospital treatment as well as patients' perceptions that the disease can be treated by a TH (Edginton et al., 2002; Liefooghe et al., 1997).

7.1.3 Delays and loss to follow-up in TB

In this PhD project, we explored patient delay and diagnostic delay in seeking healthcare from the onset of symptoms until TB diagnosis with reference to WHO framework on diagnostic and treatment delay (WHO, 2009). Patient and diagnostic delay have consequences not only to the patient but also to the surrounding community. At the individual level, delay advances the disease stage and worsens treatment outcome while at the community level, the patient can be infectious to the close contacts. It is documented that untreated TB patients can infect approximately up to 20 people annually (Dheda, 2018).

Delay in healthcare seeking in this PhD project was lower compared to other studies (Hinderaker et al., 2011b; Mfinanga and Mutayoba, 2008a; Storla et al., 2008). However, we have confirmed that patient and diagnostic delay were substantial and still required some attention. In our intervention study it became clear that patient delay in health care seeking was associated with female gender, visits to THs and behaviour factors as smoking and alcohol abuse. Our study expands on the earlier findings documenting the factors associated with delay in healthcare seeking in Tanzania and in sub- Saharan Africa in general (Mfinanga and Mutayoba, 2008a; Ngadaya et al., 2008a; E. R. Wandwalo and Mørkve, 2000).

Although we did not investigate the association between diagnostic delay and other factors than gender and poverty status in our first research question where we used data from the TB-DAR cohort, a study done in the same cohort did not find any association between gender and diagnostic delay (Said et al., 2017). Additionally, many studies have focused on patient and diagnostic delay however; there is little documentation on patient and diagnostic delay among the large population of the presumptive TB patients. Our study is the first to assess patient delay in presumptive TB patients in an intervention study in Tanzania.

When investigating LDFU in our intervention study, we found that women were more likely to be LDFU, and prior illness was positively associated with LDFU. When we stratified our analysis by gender, the odds of LDFU were higher among women without reaching statistical significance in the gender specific-estimates (chapter 4). Females were more concerned with the financial burden imposed on their spouses because of their illness and hence, many became LDFU. Results from a systematic review on pre-treatment loss to follow-up in middle and low income settings indicated a pre-treatment loss to follow-up ranging from 6% to 38%, particularly in Africa. Additionally, males were more LDFU compared to females (MacPherson et al., 2014a). These findings are contrary to our findings where females were more LDFU than males. Therefore, further studies are needed to substantiate our findings. Our study is the first to shed some light on the loss to LDFU among the presumptive TB patients which is the larger population seeking care for TB symptoms.

7.1.3 THs and TB in Tanzania

From this PhD work, it became clear that THs have a role to play in management of TB. Furthermore, THs have shown to be highly accepted and trusted healthcare providers in the society (Brouwer et al., 1998; Mbwambo et al., 2007). To our knowledge, we are reporting findings from the first study to be conducted in Tanzania on the role of THs in management of TB. Authors who describe the role of THs in TB management note that although THs are an important part of the healthcare provision in East Africa, documentation on their roles in the diagnosis and management of cough and TB related symptoms is scarce (Brouwer et al., 1998).

We have explored in the three districts of urban, peri-urban and rural Tanzania how practitioners diagnose and manage cough and TB related symptoms but also on the THs knowledge of TB symptoms, causes and transmission. We found that more than half of the practitioners knew how TB is transmitted but the knowledge of TB

symptoms and causes were somewhat limited and varied in the three study settings. Similararly findings a study conducted in Simanjiro Tanzania found variations on knowledge among the THs on TB symptoms and referrals for further treatment (Haasnoot et al., 2010).

One common similarity in all study areas is the willingness of the practitioners to refer patients to hospitals for further treatment if they could not treat them themselves. More attention should be paid to this finding as it could help in strengthening TB case findings in the community when the healers would refer the patients either for diagnosis or for further treatment. In turn, it will help in reducing TB transmission in the community. It is also clear that THs can help not only in managing TB but may help in serving as DOT supervisors as documented elsewhere (Wilkinson et al., 1999).

Spatial distribution of THs in the three study settings showed that overall 70% of the practitioners lived more than 1000 meters away from a referral hospital. The proportion of practitioners living more than 1000 meters was notably higher (80%) for THs in Ifakara compared to Temeke and Dar es Salaam. While our findings on distance might be shorter compared to other studies, this finding is important especially with regard to patient referral for formal treatment. Patients may not be able to have access to the formal health care providers' example hospitals even after referrals by the TH because of the long distance. As noted by (Barker R. et al., 2002), distance might be a risk factor for death and poor performance status among patients living far from the health care facilities.

7.1.4 Costs of TB care.

As presented in chapter three, costs of care in confirmed and presumptive TB patients were substantial, specifically the indirect costs. Even though presumptive and confirmed TB patients encountered substantial costs during care seeking (Kemp

et al., 2007; Veesa et al., 2018), few studies have documented the costs of care among the presumptive TB patients. Furthermore, it has been documented that the costs of care are usually higher during the pre-diagnosis phase than the diagnosis and treatment phase (Ukwaja et al., 2012). The higher indirect costs in our study were attributed to by income reduction specifically in confirmed patients and other indirect costs (i.e. costs for supplements and vitamins). Our results confirm findings from a study in Zambia that documented higher indirect costs than direct costs among confirmed TB patients (Aspler et al., 2008)

We have confirmed that presumptive and confirmed TB patients spent almost 30% of their monthly household income on health expenditure for the five visits. This is substantial for a population where the majority are employed in the informal sector with no sickness benefits or health insurance (Barter et al., 2012a). What we found was similar to the findings of (Shete P.B et al., 2015) which documented patients incurred up to 28% of their monthly household income on health expenditures. However, that study only documented the costs of care among the presumptive TB patients. These findings point towards the importance of further investigation of the costs of care among not only the confirmed TB patients but also among the presumptive TB patients in settings with a high TB burden.

Analyses stratified by sex and poverty status indicated that poor men with confirmed TB had lower direct costs compared to poor women and costs differed slightly among the poor men and women for the presumptive TB patients. Our results are somewhat similar to results obtained in Malawi (Kemp et al., 2007) that documented higher costs among men than women although they did not stratify the costs of care according to poverty status. Further research is needed especially in sub-Saharan Africa where few data exists to substantiate our findings.

7.2 Strengths and limitations

7.2.1 Overall strengths

Innovations in medical and treatment regimens are unlikely to substantially improve TB control without the contribution from socio-cultural determinants of health to successfully implement programmatic interventions (Mason PH, Degeling C, 2015). Socio-cultural determinants of health seeking behaviour are key aspects in TB case detection and disease control, but largely understudied in Tanzania and elsewhere in sub-Sahara Africa (Senkoro et al., 2015a). Furthermore, one of the END TB strategy's key principles is Pillar 1, which focuses on early diagnosis of TB, unhindered access to services and engaging patients in care (WHO, 2015b). Therefore, health care seeking plays a key role in disease prognosis, case detection, and proper utilization of health facilities, diagnostic procedures, and programme awareness of health options. This PhD project has shed some light on the role of socio-cultural determinants of health as well as healthcare seeking by examining pathways to care and costs of care basing on gender and poverty status. Furthermore we have explored the role of THs on TB management and control as well as explaining delay and LDFU in presumptive and TB patients.

A further strength of this project is the opportunity to investigate pathways to care not only in confirmed patients but also in presumptive TB patients. Different patient pathways to care are an important part in recognition of public health interventions in TB control. This PhD project is important because so far, most studies have been focusing on patients who are diagnosed and on treatment, rather than the large presumptive population seeking care for TB symptoms (Shete P.B et al., 2015). Finally, most studies addressing loss to follow-up (LTFU) consider TB patients in treatment, negleting the larger group of people with presumptive TB symptoms who have not yet been diagnosed and not yet started treatment.

7.2.2 Added benefits of gender perspective in TB

As mentioned throughout this PhD project, the role of gender in TB is taken into account: investigating the health-seeking behaviour including delay in seeking care, LDFU, as well as costs of health-care seeking from onset of symptoms to TB diagnosis. Understanding gender differences is important since sex and gender are both important determinants of health. Biological sex and socially constructed gender interact to produce differences not only to ill-health but also on the health-seeking behaviour and health outcomes for both men and women (WHO, 2005a). As (Johansson et al., 2000b; WHO, 2005a) clearly point out, there are very few studies on health care seeking in TB that ascertain gender differences. Sex and gender have been acknowledged as factors of importance in understanding patterns of diseases as well as providing insights into TB prevention programs and TB control (Chan-Yeung et al., 2002). Despite the widespread recognition of these differences, they have not adequately been addressed (Chan-Yeung et al., 2002; Diwan and Thorson, 1999). The strength of our study is that we report gender differences in healthcare seeking from the onset of TB symptoms together with the costs of care until TB diagnosis for both confirmed and presumptive TB patients. We believe our results are not only useful and potential in future TB research but also make a significant contribution to the literature.

Data from the intervention study offered a unique opportunity to investigate LDFU while reflecting on gender differences where very little data exist. This work may further inspire research investigating gender differences especially building on the intervention studies.

7.2.3 Added benefits on role of TH in TB management and control

As explained in section five, THs are important healthcare providers in African communities apart from the formal health care system, yet there is limited

information regarding their role (Gessler et al., 1995b). Different perspectives on TB and approaches used in TB management from urban, peri-urban and rural Tanzania are addressed including: knowledge of the THs on causes and TB transmission, management of cough and TB related symptoms, costs of TB treatment, as well as collaboration with either the government or other stakeholders. By investigating the role of THs, we were able to reveal some important findings. Knowledge of the THs concerning TB was limited and different ways were used in managing cough and TB related symptoms. Referrals for further treatment depended on the effectiveness of the prescribed traditional medicines, and women visited THs more than men. Additionally, surveying the role of THs is important in understanding different mechanisms which can be used to decrease delay in the community but also help in positive treatment outcomes since THs may act as DOT supervisors (Wilkinson et al., 1999).

Additionally, there are fewer studies that have investigated the role of THs in TB management especially in Tanzania. Findings from this study might serve as the basis of information for future projects/research to evaluate the potential for the contribution of THs and their remedies to improve TB situation in Tanzania.

7.2.4 Limitations

As we retrospectively collected data on pathways, delay and costs of care, we relied on self-reporting of delay in seeking care. Reporting errors are is likely to happen. For the LDFU study, presumptive and confirmed patients had to recall the number of days since the onset of symptoms until first health care seeking. Patients may underreport the delay because of unfriendly fear of reaction from the healthcare providers. As expressed in our findings from the qualitative research. On the other hand, confirmed and presumptive patients had to report retrospectively the costs of care from the onset of symptoms to TB diagnosis. This may have introduced

overestimation or under estimation of costs. Additionally, patients could overestimate costs of care thinking they will be compensated. Such inconsistences have been reported in other similar studies (Said et al., 2017; Ukwaja et al., 2013b). However, we tried to reduce this by relying on experienced clinical workers with extensive knowledge on data collection to interview the patients. Secondly we used visualisation charts to reconstruct the pathways to care.

Since we mainly focused on delay among the confirmed and presumptive TB patients rather than delay from the perspective of the healthcare provider, a possible limitation is in answering the broader question on the delay caused by the health systems (health system delay /provider delay).

We were able to estimate costs of care only in urban settings and not in the rural settings where the majority of the marginalized population is found. For the marginalized population these costs could be pronounced if the patients may have spent a higher proportion of their household income on health care compared to the patients in the urban population (Russell, 2004). Therefore, inclusion of the rural setting in our study might have provided a more comprehensive assessment. Tanimura et al (2014) also found considerable variations in the financial burden of TB both between individuals in the same setting and between settings. Moreover, we were only able to only investigate the costs of care from the onset of symptoms to TB diagnosis and not during the TB treatment and post-treatment periods. Additionally, we only addressed the costs of care until TB treatment in public health facilities. We might have missed out costs of care for the patients who had their final diagnosis in private health care facilities. It would be interesting for future research to investigate costs of health care seeking from the onset of symptoms to the post-TB treatment period not only in public health care facilities but also in private health care facilities.

As for the THs, our sample size was rather small (90 THs in urban, per-urban and rural setting) and we were not able to collect data from the patients who were treated with the THs. We therefore may have left out some crucial information on the patient side that could have contributed further to the body of knowledge.

7.3 Implications for research

Gender differences during pathways to care and on the costs of TB diagnosis for both the confirmed and presumptive TB patients are evident. Moreover, understanding how the poor and non-poor patients finance TB diagnosis is important (Kemp et al., 2007; Krishnan et al., 2014). Nevertheless, to the best of our knowledge, very few studies have been conducted in sub- Saharan Africa on pathways and costs of care for both confirmed and presumptive TB patients, accounting for both poverty status and gender differences, from the onset of symptoms to post-TB treatment. A few previous studies have only focused either on presumptive TB patients without taking into consideration poverty status and gender differences (Shete P.B et al., 2015) or have only focused on costs of care taking into account poverty status and gender in only confirmed patients (Kemp et al., 2007). Future studies should further investigate the pathways and costs of TB care for both presumptive and TB patients while taking into account poverty status and gender differences, not only from the onset of symptoms to TB diagnosis but also during TB treatment and post-TB treatment. Moreover, were not able to estimate the costs of TB and other co-morbidities like HIV or diabetes. We believe that the co-morbidities may have caused higher costs in both the confirmed and presumptive patients. Therefore, future research should consider co-morbidities like HIV when estimating patient's costs.

The association between LDFU and female gender in our study is in contrast to other studies which have documented that men are more LTFU than females (MacPherson et al., 2014a). Odds of patient delay were higher in females than in males. Future studies should investigate on the gender specific barriers to health

care particularly those relating to social roles. As the odds for delay were higher in women than in men and females were more LDFU than males, the feasibility and usefulness of integrating TB diagnostic services with maternal and child health care should also be explored.

The pathways to care in confirmed and presumptive TB patients in Tanzania is characterised with patients presenting themselves to the health care facilities for diagnosis and treatment as our findings revealed and as documented elsewhere (Ministry of Health and Social Welfare, 2016a). The effectiveness of active case findings should be investigated to complement the passive case findings.

The finding that THs use different traditional medicines e.g. herbs that have proven to be successful in treatment of not only coughs but also TB related symptoms, warrants further research. The efficacy of traditional medicines that treat cough and TB related symptoms should be evaluated not only in the laboratory settings but also in clinical trials.

7.4 Implications for policy and practice

I. Improved engagement between the public and private health care sectors and other stakeholders. The finding that confirmed and presumptive TB patients have complex pathways to care and that some start health care seeking at private health care facilities, underscores the importance to further include the private health care sector in TB control strategies. As the first point of care plays a major role in early TB diagnosis which appears to be a major challenge in TB control, improved engagements and collaborations between the private and public sectors is warranted so as to reduce the complexities of the pathways to care among confirmed and TB patients. Ensuring integration among the private and public health sectors will also encourage referrals of patients with TB symptoms to TB diagnostic units.

II. **Social protection against direct and indirect costs and removal or decreasing of user fees.** We found that confirmed and presumptive patients have a high financial burden during health care seeking from the onset of symptoms to TB diagnosis. Social protection schemes are needed to reduce the economic burden of TB especially in marginalized populations so as to ensure universal health coverage. Reducing economic barriers to TB diagnosis (e.g., user fees) would guarantee early care seeking among the confirmed and presumptive TB patients. Other social support packages such as foodstuff and cash transfers should be considered.

III. **More attention should be paid to gender specific needs in healthcare**. Delay and LDFU in our intervention study was substantial especially for women. Women reported seeking care at informal health care providers (e. g., THs). Given that women in particular reach clinical treatment services through a circuitous circle preferring to seek health care from THs (Johansson et al., 2000b). Although we did not find any association with regards to delay and LDFU among men, never the less, men also face barriers when assessing health care as noted in a systematic review on LMIC (Horton et al., 2016). Attention should be paid to both men and women heathcare behaviour and TB control interventions should focus on gender-specific patient needs.

IV. **Involvement of traditional healers in the educational activities of NTLP programmes.** Our findings showed minimal collaboration among the THs and the formal health-care providers as NTLP. The THs were also ready to refer patients to formal health care facilities for further treatment. This underscores the need to train and educate THs on how to recognize symptoms of TB so that they can further refer patients for timely diagnosis in health care facilities.

7.5 Conclusion

This project is among the few to report pathways to care, costs of care, determinants of delay and LDFU as well as the role of THs in TB management and control in

Tanzania. We found that the pathways to care are complex, especially in confirmed TB patients compared to presumptive patients, and that all patients incurred substantial indirect costs from the onset of TB symptoms until TB diagnosis. The odds of patient delay were higher in women than men and LDFU was associated with women. THs had limited knowledge on TB related symptoms, limited collaborations with formal health- care providers and referred patients mainly for diagnosis further treatment. Given the importance of TB in terms of global disease burden, and the WHO's ambitious goal to end TB by 2035, planning and specific interventions which integrate social and biomedical solutions are necessary in order to end the epidemic

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Appendices

Appendix 1. CRF 12 Pathways to care

CRF 12: Pathway to care (Objective 1 PhD Grace)			
Section 1 : Patients Information			
	Date of interview	|___|___| |___|___| |___|___|___|___|	*DD/MM/YYYY*
	Patient ID and visit	|___|___|___|___|___|-|___|___|-|___|___|___|	*Scan from the barcode for the specified visit. i.e. VO1, VO2, VO3*
Section 2: Socioeconomic status			
	Education level	☐ No formal education ☐ Accomplished primary school education ☐ Accomplished secondary school education ☐ Accomplished college/university	*Select one*
	How many years in total have you spent in school or in full time study?	_____	*In figures*
	Current employment status	☐ Unemployed ☐ Petty trader ☐ Carpenter ☐ Business person ☐ Student ☐ Retired /long-term disabled	*Select one*
	House ownership	☐ Your own ☐ Rented ☐ Rented, but paid by somebody else	
	Household monthly income	_____	*In thousands Tanzanian shillings*
	Household size	|__|__|	*How many people currently living in your household*
	How many people older than 18 years, including yourself, live in your household	|__|__|	
	Household contribute	|__|__|	*All household members (patient included) that contribute to living expenses*
	How many rooms used for sleeping	|__|__|	
	How many people sleep in each room	|__|__|	
	Do you own a piece of land	☐ Yes ☐ No	
	House has electricity	☐ Yes ☐ No	
	Floor type	☐ earth sand ☐ cement ☐ tile ☐ other	*Select one*
	Walls type	☐ Grass ☐ mud ☐ sundried bricks ☐ baked bricks ☐ wood timber ☐ cement ☐ stones ☐ other	*Select one*
	Roof type	☐ Grass, thatch or mud ☐ iron sheet ☐ concrete ☐ asbestos ☐ other	
	Do you have a radio?	☐ Yes ☐ No	
	Do you have a TV?	☐ Yes ☐ No	
	Do you have a mobile phone?	☐ Yes ☐ No	

	Does your home have a refrigerator?	☐ Yes ☐ No	
	Do you have a bicycle?	☐ Yes ☐ No	
	Do you have a motorcycle?	☐ Yes ☐ No	
	Do you have a car or a truck	☐ Yes ☐ No	
Section 3: Knowledge and perception of TB			
	Do you know about TB disease	☐ Yes ☐ No	
	If yes, where did you learn about it	☐ From health care worker ☐ From school ☐ from a friend ☐ From a family member at home ☐ From media (magazine, radio television) ☐ Others Other types of learning not listed, please specify (comma separated)	*multiple answers*
	What causes TB	☐ Bacteria ☐ Dust ☐ Contact with infected person ☐ Prior illness ☐ Smoking, ☐ Air borne illness Other causes not listed, please specify (comma separated) _____	*multiple answers*
	Is TB contagious	☐ Yes ☐ No	
	TB is mostly commonly transmitted from person to person in which of the following ways	☐ Blood/bodily fluids ☐ Air ☐ Food ☐ Shared objects ☐ Others Other types of transmission not listed, please specify (comma separated) _____	*multiple answers*
	What was the first symptom that you encountered	Productive cough ☐ fever ☐ hemoptysis ☐ night sweat☐ chest pain ☐ weight loss ☐ abdominal pain	
	Do you think anyone with TB must have HIV infection?	☐1 ☐2 ☐3 ☐4 ☐5	*1 strongly agree* *5 strongly disagree*
	Do you know the importance of coughing in an open air	☐ Yes ☐ No	
	Do you have any knowledge about sputum production and submission	☐ Yes ☐ No	
	If yes where did you learn	☐ From health care worker ☐ From school ☐ From a friend ☐ From a family member at home ☐ From media (magazine, radio television) ☐ Others Other types of learning not listed, please specify (comma separated) _____	*multiple answers*
	Common symptoms of pulmonary TB includes	☐ Cough ☐ Diarrhea ☐ Night sweats ☐ Fever ☐ Nausea/vomiting ☐ Weight loss ☐ Hemoptysis ☐ breathlessness ☐ others Other common symptoms not listed, please specify (comma separated) _____	*multiple answers*
	Is TB curable	☐ Yes ☐ No	
	If yes How is it cured	☐ Cough medicine ☐ Injections ☐ Tablets for TB ☐ Tablets Other treatments not listed, please specify (comma separated) _____	
Section 3: Health care seeking behavior			
	What was the first symptom that you encountered	Productive cough ☐ fever ☐ hemoptysis ☐ night sweat☐ chest pain ☐ weight loss ☐ abdominal pain	
	How long have the symptoms been persisting	Productive cough _____ (weeks) Fever _____ (weeks) Night sweats _____ (weeks) Hemoptysis _____ (weeks) Chest pain	

		_____ (weeks) Weight loss _____ (weeks)	
	Did you seek care for your symptoms	☐ Yes ☐ No	
	When was the first contact with the health care facility	_____ (weeks)	
	Where did you seek care for the first symptoms that you encountered	☐ Private/governmental hospital ☐ Pharmacy ☐ Dispensary ☐ Local home remedies/non-professional friends ☐ Traditional healer ☐ Religious healer ☐TB clinic ☐Primary Health care Other types of health care seeking not listed, please specify (comma separated) _____	*multiple response*
	How far is the place that you first sought care from your home	☐ minutes walking ☐ minutes with transport _____ minutes _____	
	How far is the nearest government facility for TB diagnosis only	☐ walking ☐ with public transport _____ minutes _____ (minutes)	
	How far is the nearest government facility for TB diagnosis and treatment	☐ walking ☐ with public transport _____ minutes _____ (minutes)	

Section 4: Pathway of care (Visualization chart will be presented to the patients as a proxy)

1st Visit	**Location** ☐ Hospital ☐ Pharmacy ☐Dispensary ☐ Local home remedies/non-professional friends ☐ Traditional healer ☐ Religious healer ☐ TB clinic ☐ Primary health care ***Select from the GPS Codes***	**Symptoms** Symptoms _____weeks ago Presumptive diagnosis made during the visit ☐ Pneumonia ☐ Bronchitis ☐ Upper respiratory illness ☐ TB suspected ☐ Unknown ☐ Other _____	**Medication** Medication given ☐ Amoxicillin ☐ Ciprofloxacin ☐ Ceftriaxone ☐ Home remedies ☐ Traditional medicine ☐ Ampiclox ☐ Cough Syrup ☐ Cephalexin ☐ Unknown ☐ Other _____	**Estimated direct costs** ☐ Medical costs Tsh _____ ☐ Transport expenses Tsh _____ ☐ Diagnostic costs Tsh _____ ☐ Informal payments Tsh _____ ☐ Food expenditures and accommodation Tsh _____ ☐ Unknown Tsh _____ ☐ Other direct costs specify _____ Tsh _____	**Estimated indirect costs** ☐ Income reduction Tsh _____ ☐ Decrease productivity Tsh _____☐ Copying Costs Tsh _____☐ Less paid labor Tsh _____ ☐ Unknown Tsh _____ Other indirect costs specify _____ Tsh _____
2st Visit	**Location** ☐ Hospital ☐ Pharmacy ☐Dispensary ☐ Local home remedies/non-professional friends ☐ Traditional healer ☐ Religious healer ☐ TB clinic ☐ Primary health care ***Select from the GPS Codes***	**Symptoms** Symptoms _____weeks ago Presumptive diagnosis made during the visit ☐ Pneumonia ☐ Bronchitis ☐ Upper respiratory illness ☐ TB suspected ☐ Unknown ☐ Other _____	**Medication** Medication given ☐ Amoxicillin ☐ Ciprofloxacin ☐ Ceftriaxone ☐ Home remedies ☐ Traditional medicine ☐ Ampiclox ☐ Cough Syrup ☐ Cephalexin ☐ Unknown ☐ Other _____	**Estimated direct costs** ☐ Medical costs Tsh _____ ☐ Transport expenses Tsh _____ ☐ Diagnostic costs Tsh _____ ☐ Informal payments Tsh _____ ☐ Food expenditures and accommodation Tsh _____ ☐ Unknown Tsh _____ ☐ Other direct costs specify _____ Tsh _____	**Estimated indirect costs** ☐ Income reduction Tsh _____ ☐ Decrease productivity Tsh _____☐ Copying Costs Tsh _____☐ Less paid labor Tsh _____ ☐ Unknown Tsh _____ Other indirect costs specify _____ Tsh _____

3rd Visit	**Location** ☐ Hospital ☐ Pharmacy ☐Dispensary ☐ Local home remedies/non-professional friends ☐ Traditional healer ☐ Religious healer ☐ TB clinic ☐ Primary health care ***Select from the GPS Codes***	**Symptoms** Symptoms _____weeks ago Presumptive diagnosis made during the visit ☐ Pneumonia ☐ Bronchitis ☐ Upper respiratory illness ☐ TB suspected ☐ Unknown ☐ Other _____	**Medication** Medication given ☐ Amoxicillin ☐ Ciprofloxacin ☐ Ceftriaxone ☐ Home remedies ☐ Traditional medicine ☐ Ampiclox ☐ Cough Syrup ☐ Cephalexin ☐ Unknown ☐ Other _____	**Estimated direct costs** ☐ Medical costs Tsh _____ ☐ Transport expenses Tsh _____ ☐ Diagnostic costs Tsh _____ ☐ Informal payments Tsh _____ ☐ Food expenditures and accommodation Tsh _____ ☐ Unknown Tsh _____ ☐ Other direct costs specify _____ Tsh _____	**Estimated indirect costs** ☐ Income reduction Tsh _____ ☐ Decrease productivity Tsh _____☐ Copying Costs Tsh _____☐ Less paid labor Tsh _____ ☐ Unknown Tsh _____ Other indirect costs specify _____ Tsh _____
4th Visit	**Location** ☐ Hospital ☐ Pharmacy ☐Dispensary ☐ Local home remedies/non-professional friends ☐ Traditional healer ☐ Religious healer ☐ TB clinic ☐ Primary health care *Select from the GPS Codes*	**Symptoms** Symptoms _____weeks ago Presumptive diagnosis made during the visit ☐ Pneumonia ☐ Bronchitis ☐ Upper respiratory illness ☐ TB suspected ☐ Unknown ☐ Other _____	**Medication** Medication given ☐ Amoxicillin ☐ Ciprofloxacin ☐ Ceftriaxone ☐ Home remedies ☐ Traditional medicine ☐ Ampiclox ☐ Cough Syrup ☐ Cephalexin ☐ Unknown ☐ Other _____	**Estimated direct costs** ☐ Medical costs Tsh _____ ☐ Transport expenses Tsh _____ ☐ Diagnostic costs Tsh _____ ☐ Informal payments Tsh _____ ☐ Food expenditures and accommodation Tsh _____ ☐ Unknown Tsh _____ ☐ Other direct costs specify _____ Tsh _____	**Estimated indirect costs** ☐ Income reduction Tsh _____ ☐ Decrease productivity Tsh _____☐ Copying Costs Tsh _____☐ Less paid labor Tsh _____ ☐ Unknown Tsh _____ Other indirect costs specify _____ Tsh _____

TB-PHARM STUDY

DELAY IN SEEKING CARE AND LOSS TO FOLLOW UP FOR TB SUSPECTS (EMIC) INTERVIEW.

(EMIC) INTERVIEW.)

English Version5/08/2015.

Ifakara Health Institute and Grand Challenge Canada**.**

Appendix 2. Delay in seeking care and loss to follow up for TB suspect's refereed from pharmacies questionnaire

EMIC ID

Date of Interview (DD-MM-YY)

Pharmacy

1 Kiomboi	2 Mtakuja	3 Mnyamani	4.Mandela	5.Henrick	6.Buguruni hospital.

Introduction

" Thank you for taking your time and participate in this study. I would like to ask you a few questions about your background, the kind of ideas you have about the problems that brought you to the pharmacy and the help you have taken for it so far. There are no right or wrong answers to these questions. Please feel free to tell me your own ideas, what you really think about your problem. But first, a few questions about your background"

Socio-economic and demographic information

Sex and age

Sex	F	M

Approximate age (years)

Household size

Number of people living in your household

Marital status.

Tick one only:

☐ 1. Never married
☐ 2. Married
☐ 3. Separated
☐ 4. Divorced
☐ 5. Living together
☐ 6. Widowed
☐ 7. Cannot say/ Not disclosed

Children living in the household *(0=None)*

Number of children	**< 5 yrs**	**5-10 yrs**	**10-17 yrs**
Sons			
Daughters			

Relationship with household head

Tick one only:

☐ 1. Self
☐ 2. Spouse
☐ 3. Parent
☐ 4. Sibling
☐ 5. Son or daughter
☐ 6. Other; Specify_____

Tick sex of household head:

☐ 0. Female ☐ 1. Male

Main occupational status

Tick one only

☐ 1. Agriculture
☐ 2. Fishing
☐ 3. Self employed
☐ 4. Formally employed
☐ 5. House maid
☐ 6. House wife
☐ 7. Casual laborer
☐ 8. Student
☐ 9. Not active/ retired
☐10.Other; Specify_____

Education attained

Tick highest completed level:

☐ 0. No formal education
☐ 1. Primary education
☐ 2. Secondary education
☐ 3. Vocational training
☐ 4. College education

Years spent in education/ training: _____years.

Otherwise tick if you cannot say ☐

Religion

Tick one only:

☐ 1. Muslim
☐ 2. Christian
☐ 3. Other; Specify_____
☐ 4. Undisclosed

Nationality Tick *one only:*

☐ 0. Tanzanian

☐ 1. Other; Specify_____

"Is your household income usually reliable (and dependable)?"

Tick one only.

☐ 3. Yes
☐ 0. No

☐ 2. Possibly
☐ 1. Uncertain/not disclosed

Narrative: _____
_____
_____
_____

"What main sources of income are there in your household?"

Narrative:

_____
_____
_____

Query for items not mentioned (except the last two), tick all that apply:

Sources of income	**Own**	**Others**
1 Employment for cash		
2 Employment in kind		
3 Non-farm self-employment		
4 Selling agricultural produce		
5 Selling fish and seafood		
6 Rent		

Sources of income	Own	Others
7 Remittances (money sent from outside)		
8 Other specify:		
9 Cannot say		

"How much money did you make during the last month on your own? And what about your spouse and other household members?"

Narrative:

_____

_____

Query for items not mentioned, clarify if needed

Monthly Income	Tsh	Cannot say
1.Own		
2.Spouse		
3.Other household member		

Clinical History And Illness experience.

I will now ask you about the problem that led you to seek help. Later, I will ask you about what has been helpful for it in the past and what you feel might now be helpful. While doctors have special ways of understanding illness, people like yourself also have their own ideas, which may be different from what doctors think. It will help us to help people with problems like yours by understanding how your problem has affected you, what it means to you, and what you do to get help for it."

Open Ended Enquiry

1.1 "What is the problem for which you sought help: Please tell us about it."

Narrative: _____

_____

Patterns of distress (associated symptoms and impact on life)

In addition to the problem that you have mentioned, are there any other symptoms that that have troubled you or that you are concerned about?

Narrative: _____

_____

Tick all that apply

Physical symptoms tick

1. Cough		6. Loss of appetite	
2. Fever		7. Weight Loss	
3. Chest Pain		8. Side effects	
4. Blood in sputum		9.Other physical Symptoms _____	
5. Breathlessness			

1.2 Effects on life

"How does this problem (do these problems) affect your life?

Narrative: _____

_____

Perceived **causes**

2.1 "Each of us may explain our health or health problems in various ways. What do you think has caused this problems?"

Summarize the respondent's ideas about causes in the respondent's own words:

Narrative: _____

_____

"Based on the patient's account, mark perceived causes in the "spon" column that are reported spontaneously in response to the open-ended question

Continue by probing for any perceived causes not yet mentioned from the major subgroups listed below. Screening each item, mark additional perceived causes reported in response to "probe."

Perceived Cause	**Spon**	**Probe**
1 Food		
2 Water		
3 Alcohol		
4 Smoking		
5 Air borne illness		
6 Heredity		
7 Contamination		
8 Sexual Contact		
9 Climate		

Perceived Cause	**Spon**	**Probe**
10 Dust		
11 Contact with infected person		
12 Prior Illness		
13 Evil eye, sorcery		
14 Demons or Gods		
98 Others, Specify _____		
99 Can not say		

2.2

If patient has mentioned more than one cause of the problem, inquire further:
"Which of these causes that you have mentioned (or perhaps something else) do
You now consider the most important cause of your problem?"

Narrative: _____

_____

Code single most important perceived cause from the above list of perceived causes

Health seeking.

2.3 "We realize that you have come here for help, but many people who come here have also sought help from many other sources also. This is certainly understandable and not something you should be embarrassed about. We would like to know what kinds of help you have sought out before coming here for this particular problem? Please tell us about all the things you did and people you consulted for help since the beginning of this problem."

Narrative: _____

_____

For each of the following sources of help, mark whether patient reported use, either spontaneously in response to the open-ended query or in response to probe. **Help Seeking List.** _____

Help Seeking list.	**Spont**	**Probe**
1. Home remedies, self-care, family, or non-professional friends		
2. Drug stores (Pharmacies)		
3. Private or governmental hospital		
4. Traditional healer		

Help Seeking list.	**Spont**	**Probe**
5. Primary health care center (dispensary)		
6. Religious healer		
7.This Clinic		
8.TB clinic		
9. Other		

2.4 "From the list of sources that you sought care, Tell me the sequence of providers in the order that you consulted them. How many times did you see each of them?"

Sequence	1	2	3	4	5	6	7	8	9
4. Traditional Healer									
5.Primary health care center (dispensary)									
2.Drug stores (Pharmacies)									
3.Private or governmental hospital									
8.TB Clinic									

Narrative _____

_____

First Help Seeking

Inquire about first help excluding home remedies and self-care:

2.5 "What was the first help you sought for this problem outside your home, other than from friends and family?"

Narrative _____

_____

_____

2	Drug store
3	Hospital
4	Traditional healer
5	Primary health care center (Dispensary)
6	Religious healer
7	This Clinic
8	TB Clinic
9	Other

Code first help seeking type from categories in above list. ☐

Reasons for choice

2.6 "What was the main reason that led you to decide to get help from this place you went to first rather than some other place?"

place you went to first, rather than some other place?"

Narrative _____

_____

_____ "How long was it after your problem began that you went to the pharmacy for help?"

Narrative _____

_____

_____

3. One day to one week	3 More than two weeks	1. Months

2.7 "How many times did you go to the pharmacy to seek care?"

Narrative _____

_____

_____

1. One Time	2. Two Times	3. Three times	4. >Three times

2.8 "What led you to wait before seeking care at the pharmacy for your problem?"

Narrative _____

_____

_____

2.9 "How did you go? By what means of transport?"

Narrative _____

_____

_____

Tick all that apply

1.By a daladala (bus)	
2.By feet	
3.Private car	
4.Bicyle	
5.Bajaji	
6.Other specify	

2.10 "What was the cost of travel to reach there?"

TSh ☐

2.11 “What kind of treatment did you get from this provider?”
Narrative _____
_____
_____

Tick all that apply

1. Cough medicine	
2. Tablets	
3. Injection	
4. Tablets for TB	
5. Cannot say	

2.12 “Were you satisfied with the care you received?”

Narrative _____
_____
_____

3.Satisified	2.Somehow satisfied	1Not satisfied	0 Don’t know

2.13 “What did this person whom you first went to for help tell you about your problem? By what name did he (or she) call it?”

Specify name, summary term, or short description in the patient's words. Provide English meaning if appropriate If “other,” specify term and explain here

Narrative _____
_____
_____

Specify exact term used: _____

Identified as TB?

1 Yes	2 No

Loss to follow up (patients with presumptive TB**)**

We appreciate your account of the reasons and experience in using the pharmacy. Was there some reason, however, that you did not go directly to a TB clinic?”

3.1 “Was it a strain for you to travel for health care for your problem beyond the pharmacy?”

Tick one only

3 Yes	2 Possibly	1 Uncertain	0 No

Narrative _____
_____
_____

3.2 “Did you feel embarrassed to go for further medical care after your visit to the pharmacy?”

Tick one only

3 Yes	2 Possibly	1 Uncertain	0 No

Narrative _____

_____

3.3 “Did the pharmacist, or anyone else explain the importance of seeking further health care? Were you told clearly enough so that you could understand?”

Tick one only

3 Yes	2 Possibly	1 Uncertain	0 No

Narrative _____

_____

_____

3.4 “Did you have any concern that your family might not like it, or might not support you if you went for further help in the hospital?”

Tick one only

3 Yes	2 Possibly	1 Uncertain	0 No

Narrative _____

_____

3.5 “Has getting further help beyond the pharmacy added to the burden of your illness on your family?”

Tick one only

3 Yes	2 Possibly	1 Uncertain	0 No

Narrative _____

_____

3.6 “Were you afraid the doctors or health staff might tell you that you have TB if you went to the health facility?”

Tick one only

3 Yes	2 Possibly	1 Uncertain	0 No

Narrative _____

_____

Concluding advice from patient

4.1 Do you have any ideas or suggestions about what might make it easier for people with symptoms like yours to get the help and treatment they need?”

Narrative _____

Interviewer (name/signature)	
Recorder (name/signature)	
Narratives translated & typed (date)	
Controlled (date/initials)	
1st Data entry (date/initials)	
2nd Data entry (date/initials)	

Additional comments from the interview team

Notes concerning the participant's interest and the quality of the interview, and other noteworthy features and details of this interview:

Appendix 3. Traditional healers Quantitative questionnaire

Traditional healers (systematic questions)			
Section 1: Contact Information			
	Date of interview	|___|___| |___|___| |___|___|___|___|	*DD/MM/YYYY*
	Name of the traditional healer ***Select from the GPS Codes (if available)***	_____ _____	
	Place of work ***Select from the GPS Codes (if available)***	☐ Temeke ☐ Ifakara ☐ Bagamoyo _____ (Sub district/street/ten cell)	
Section 2: Traditional medicine and practices			
	Have you treated anyone with coughing or other symptoms suggestive of TB	☐ Yes ☐ No	
	Type of medication given to patients with cough symptoms/TB	☐ Medicinal plants (herbs) specify name (Select from the menu) _____ ☐ holy water and laying of hands ☐ Casting spell and use of poppets ☐ Charms Other types of treatment not listed, please specify (comma separated) _____	
	How many patients with cough symptoms do you see in a day	_____no of patients	
	How long does it take to treat each patient	_____ no of days	
	How long does the patient stay at your place for treatment on average	_____Weeks	
	How many sessions	_____sessions	

	do you usually have with the patient during the treatment period		
	If the treatment does not work what do you usually do?	☐ Referral to the hospital ☐ Referral to the pharmacy ☐ Referral to a nearby dispensary ☐ Change of medication type and practice ☐ Referral to a more experienced traditional healer Other _____	
	After how long do you refer the patient for other treatments (on average)	_____Weeks	
	Do you sleep in the same house with a patient if you admit them for treatment	☐ Yes ☐ No	
	Do the cough/TB symptoms improve after treatment	☐ Yes ☐ No	
	How long does it take for the cough symptoms to improve (on average)	_____Weeks	
	How long does it take for the patient to be completely cured (on average)	_____Weeks	
	How much do you charge for a single session with the patient	_____ Tsh (on average)	
	How much do you charge in total for treatment to a single patient	_____ Tsh (min / max range)	
	Do you do your work in open environment?	☐ Yes ☐ No	
	Do you treat any other diseases apart from cough / TB symptoms	☐ Yes ☐ No	
	What type of diseases do you treat	☐ Malaria ☐ HIV and STI`s ☐ Pneumonia ☐ Typhoid Others _____	

	How far is the nearest government facility for diagnosis only	☐ walking ☐ with public transport _____ minutes _____ (minutes)	
	How far is the nearest government facility for diagnosis and treatment	☐ walking ☐ with public transport _____ minutes _____ (minutes)	
	Have you ever had discussion with the government regarding your treatment practice	☐ Yes ☐ No	

Name of Interviewer

Initial / Date /

Appendix 4. Traditional healers: Qualitative questionnaire.

INTERVIEW GUIDE FOR TRADITIONAL HEALERS

Introduction

Hello. Thank you for taking your time and agreeing to participate in this interview. We will ask you some questions concerning your treatment practices and your ideas on health problems in your community. Please feel free to respond according to what you understand. There are no wrong or right answers. We would like to know your ideas and opinions. The information that you will give us will be tape recorded and kept confidential. We will assign you a special number to use as alternative of your name, to maintain confidentiality. This information will help us to know treatment practices and your knowledge concerning health problems in your community. This will then help us to inform and suggest measures to the national and international guidelines regarding the health problems in your community.

A:Traditional practices and Illness Perception

- Kindly tell us, when did you start working as a traditional healer?
- Where did you learn about traditional practices and treatment?
- What are the common health problems affecting your community that you treat? Kindly tell us all health problems you treat.

  -If s/he mention cough probe kindly explain what you know about all kind of cough problems and its symptoms.
- What is the background of the patients that you treat (probe. Economic status, level of education, sex, marital status)
- Do you only treat people with cough symptoms or any other diseases?
  - If so what kind of disease you treat.
- If someone with a sever cough comes to see you, what do you do step by step?
- How do you identify the reasons for a cough? Can you give examples for reasons and respective treatment options?
- How many patients with cough symptoms do you see and treat in a day?
- How do you treat the patient? Why? What kind of drugs do you use? Please explain step-by-step
- How long does the treatment last?
- If the patient does not get better after the treatment what do you do? Kindly explain everything that you do.

- Do you refer the patient for some other kind of treatment if the treatment fails? Please explain Where/ When and how
- Do you charge any form of payment for treatment? If yes what do you usually charge? (probe money, payment in kind)

B: Understanding of TB

- Do you know a disease called TB? If yes, please explain what you know
- Where did you get the information about the causes, symptoms and treatment of TB?
    - Probe: from health care worker, from the health care facility/TB clinic from school, from a family member, from a friend, from media ie magazine, radio television, from a fellow healer, (Others specify)
- Do you know what causes TB
- Do you know how TB is transmitted from one person to another?
- If someone develops TB symptoms what do you think should he/she do? Please explain step by step. (Probe: hospital, pharmacy, dispensary, traditional healer, local home remedies, primary health facilities). Is it useful to use different health providers? Which ones? Why?
- Have you treated anyone with TB in the past?
    - If yes, what did you do? Please explain.
- Do you think anyone with TB must have any other disease (probe, HIV, Pneumonia, Malaria)

C: Collaboration among traditional healers and the government

- Have you ever had discussion with the government regarding your treatment practice?
- Is there any collaboration between you and the government? If yes what kind of collaboration.

Do you get any form of threat or mistreatment by the government regarding your work as a traditional healer?

Curriculum Vitae

Grace Mhalu
P.O BOX 74 Dar es Salaam, Tanzania
gmhalu@ihi.or.tz
Mobile: +41 76 828 52 55 /+255 65 588 88 91
Tanzanian

Interest in Social, Public Health Evaluation Research, and Infectious diseases

Data management skills, effective communications, writing skills

Team supporter, cooperative dedicated and innovative

Professional Experience

Swiss Tropical and Public Health Institute, University of Basel 09.2015 to date

Doctoral candidate

- Research on infectious diseases tuberculosis in particular.
- Scientific manuscripts writing
- Master's students supervisor
- Grants and proposals writing to research funding institutions
- Disseminating research results through conferences, seminars and symposiums

Ifakara Health Institute Tanzania 04. 2010-July 2015

Study coordinator and research officer

- Management and coordination of tuberculosis clinical trials, cohort studies and operational research
- Data management and data analysis with Epi Info, SPSS and Stata
- Scientific manuscripts writing
- Proposals writing
- Team supervision

Education:

PhD in Epidemiology Swiss Tropical and Public Health Institute, Expected December 2018

Master of Public Health, Muhimbili University of Health and Allied Sciences, September 2014

Bachelor degree in Social Science (Sociology), University of Dar es Salaam, July 2009

Language and Skills:

English (working language C1)

Swahili (native speaker)

MS Office, SPSS, Epi Info, Stata MAXQDA F4, ODK, Arch GIS

Trainings:

Systematic reviews and meta-analyses	2016
Scientific writing	2016
Presentation skills	2017
Monitoring and evaluation	2015
Project management	2014

Publications:

- **Mhalu G**, Hella J, Doulla B, Mhimbira F, Mtutu H, Hiza H, Sasamalo M, Rutaihwa L, Rieder HL, Seimon T, Mutayoba B, Weiss MG, Fenner L. Do instructional videos on sputum submission result in increased tuberculosis case detection? A randomized controlled triial PLoS One. 2015 10(9): e0138413.
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- Mhimbira F, Hiza H, Mbuba J, Hella J, Kamwela M, Sasamalo M, Ticlla M, Said K, **Mhalu G,** Chiryamkubi M, Schindler C, Reither K, Gagneux S, Fenner L. Prevalence and clinical significance of respiratory viruses and bacteria detected in tuberculosis patients compared to household contact controls in Tanzania: a cohort study Clin Microbiol Infect pii: S1198-743X1830229-5. DOI. 10.1016J.CMI.2018.03.2019
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