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Pathways and associated costs of care in confirmed and presumptive tuberculosis patients in Tanzania: A cross-sectional study

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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.

BACKGROUND

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 [1,2]. Many patients consult various healthcare providers before being diagnosed with TB [3,4]. These pathways are usually complex and delayed diagnosis and treatment may increase morbidity and mortality [5]. 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 [6]. 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 [7,8]. 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 [9]. However, patients with symptoms of TB face high direct and indirect costs for diagnosis and treatment [10–13], and these costs are usually higher for patients with confirmed TB than presumptive cases [3,14].

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 [4,15]. 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 [14].

A national TB prevalence survey indicated that the case detection rate of TB was below 50% [16]. This result may not only be due to the complexity but also the high cost of care [15,17,18]. 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 [9,19,20].

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 [21]. Costs for presumptive cases are not well understood, especially in sub-Saharan Africa [3,22]. In addition to financial costs, sociocultural and gender-related factors can shape how patients seek healthcare [23], yet such studies of the influence of these factors are scarce [24]. Finally, only few studies have examined pathways and costs of seeking health care by comparing confirmed and presumptive TB patients [3,10,25].

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.

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 [4]. The district is densely populated with a population of 1,369,000 persons [26]. 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 [27]. 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 [28]. 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 [29].

We included adult, sputum smear-positive TB patients and presumptive TB cases who were consecutively enrolled in the TB-DAR study [4,30] between August 2016 and January 2017, until the target sample size of 100 patients in each category was reached (Figure 1). Based on power calculation and previous studies [3,25] 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.

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 [31].

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 [32]. 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 [32]. 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 [33]. 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 [33]. Diagnostic delay was defined according to the framework of WHO (29) and used in previous studies [34,35] 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 [4]. 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 [36].

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 [4]. 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 [26]. 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 [37,38]. 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 [3,14]. 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).

Patient involvement

Patients were not involved in the development, design, and analysis of this study.

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.

Availability of data and materials

According to the Institutional Review Board of the Ifakara Health Institute, we are not allowed to make the data publicly available. Interested researchers should contact the corresponding author.

Competing interest

All authors declare that they have no competing interests.

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 weeks.

Pathways to care

The spatial distribution of healthcare facilities in the study area show pharmacies and dispensaries are distributed over the whole area Figure (2A). Hospitals are situated mainly in the urban centres and traditional healers predominantly in the peripheral area. Figures (2B) and (2C) 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.

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 3). 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 patients indicated a fourth and fifth visit).

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]).

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.

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]).

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.

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 4). 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).

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 [39], and partially explains the diagnostic delay. Compared to findings of other studies [19,40] 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 [41]. 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 [35,42,43]. 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 [42].

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 [13], and expenditures for seeking healthcare for TB can cause or exacerbate poverty [44]. 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 [13]

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 [44]. 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 [11]. 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.

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 [39]. 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 [45]. These interventions are central for reaching the ambitious WHO targets of zero deaths, disease, and suffering due to TB by 2035 [46].

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Author contributions

Conceived and designed the study: GM, JH, FM, KS, PM, SG, KR, KH, TM, MGW, EZ, and LF. GM, JH, KD, YM and FM analysed the data. GM and LF prepared the first draft of the manuscript. KR, KS, PM, YM, TM, MGW, EM, EZ and LF contributed to the major revision of the manuscript. All authors contributed to final manuscript revisions and approved the final version.

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FIGURE LEGENDS

Figure 1. Flowchart of the study population. Participants were enrolled until the final target of 100 confirmed and 100 presumptive TB patients was reached.

Figure 2. 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.

Figure 3. Spine plots showing distribution of health care facility visits during the pathway of care (first, second, third and fourth/fifth visit) in confirmed and presumptive patients. Numbers on the graph indicate absolute numbers.

Figure 4. 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).

Tables and Figures

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

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.

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

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

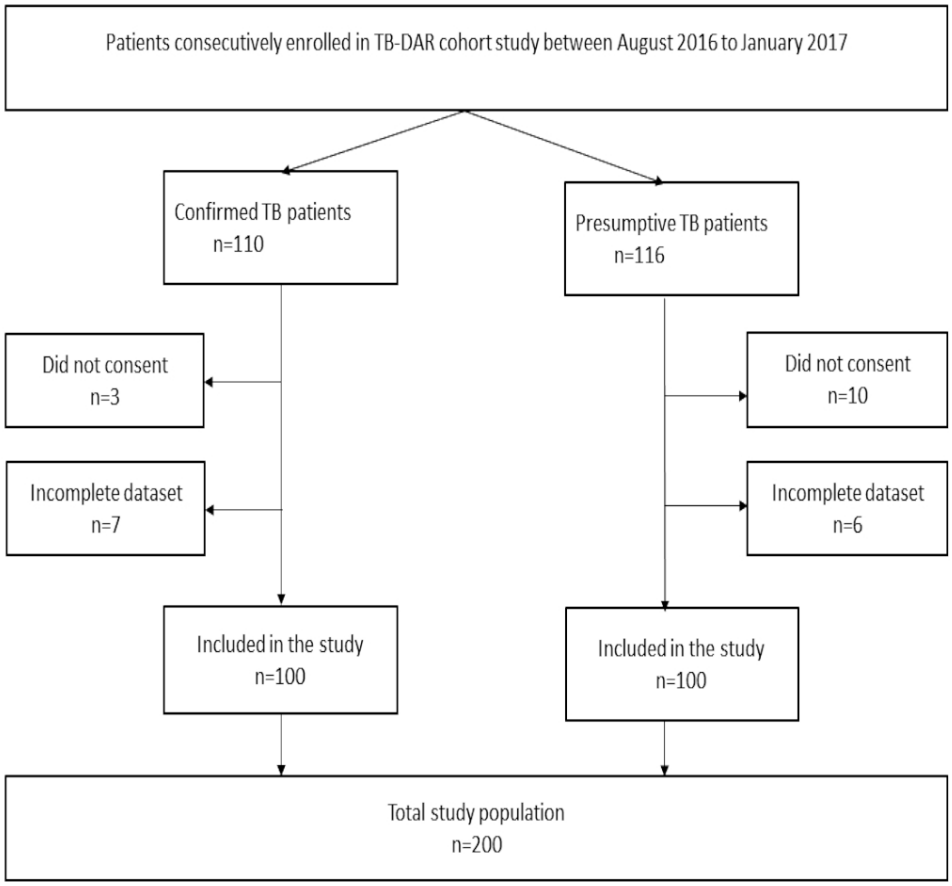
Table 5. Estimates of effects of different factors on median direct, indirect and total costs in USD among confirmed and presumptive TB patients

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 education



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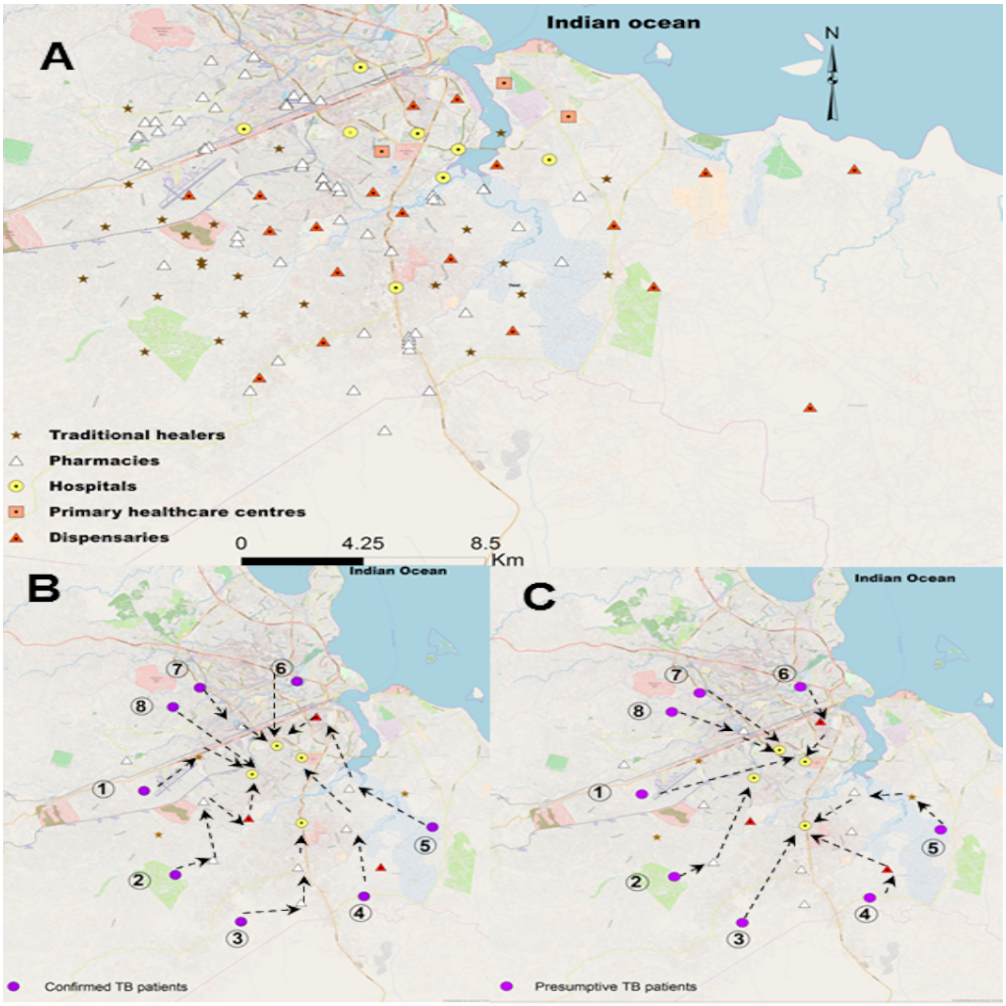

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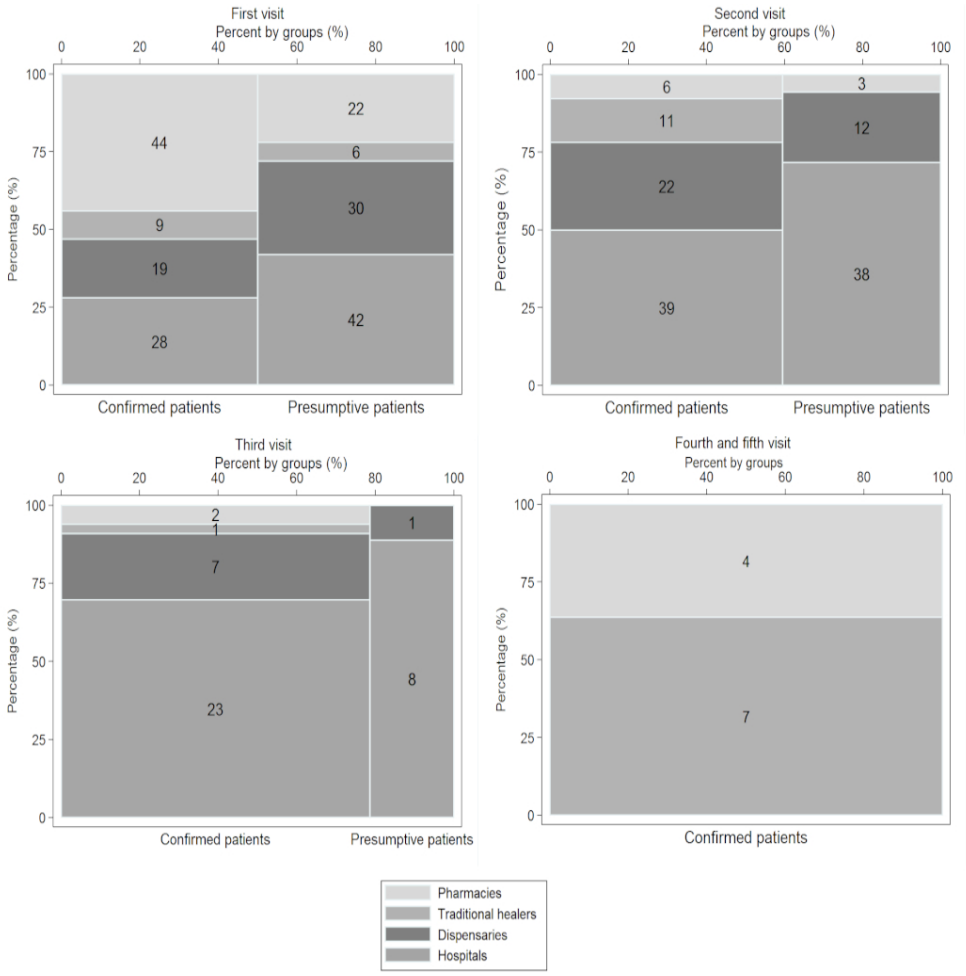

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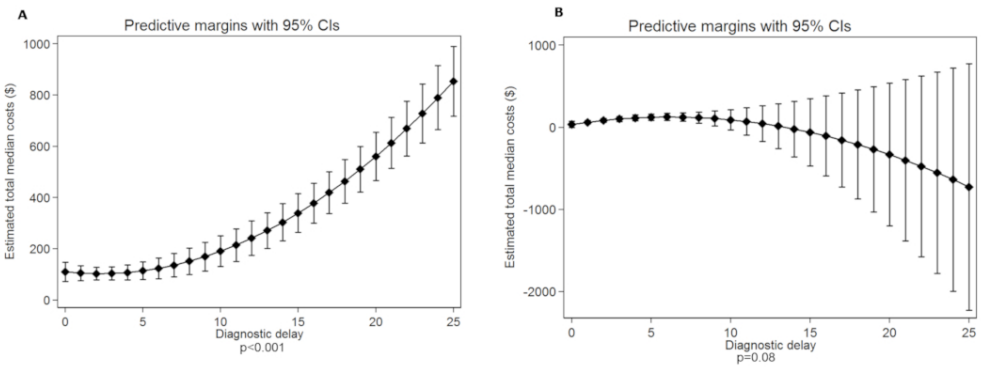

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Supplementary Table 1. Direct costs associated with first, second and >2 visits for patients with confirmed and presumptive TB.

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

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 6
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 6
Methods			
Study design	4	Present key elements of study design early in the paper	Page 7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	Page 7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 7-8
Bias	9	Describe any efforts to address potential sources of bias	Page 9
Study size	10	Explain how the study size was arrived at	Page 7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 9
		(*b*) Describe any methods used to examine subgroups and interactions	Page 9
		(*c*) Explain how missing data were addressed	-
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	-
		(*e*) Describe any sensitivity analyses	-
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Page 12
		(b) Give reasons for non-participation at each stage	-
		(c) Consider use of a flow diagram	Page 7
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	
		(b) Indicate number of participants with missing data for each variable of interest	-
Outcome data	15*	Report numbers of outcome events or summary measures	Page 13
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	-
		(*b*) Report category boundaries when continuous variables were categorized	-
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Page 14
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 17
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 20
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 17-20
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 17-20
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 22

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Pathways and associated costs of care in confirmed and presumptive tuberculosis patients in Tanzania: A cross-sectional study

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TITLE PAGE:

Pathways and associated costs of care in confirmed and presumptive tuberculosis patients in Tanzania: A cross-sectional study

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Inserts:

4 figures and 5 tables, Supplementary File (3 tables)

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.

BACKGROUND

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 [1,2]. Many patients consult various healthcare providers before being diagnosed with TB [3,4]. These pathways are usually complex and delayed diagnosis and treatment may increase morbidity and mortality [5]. 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 [6]. 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 [7,8]. 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 [9]. However, patients with symptoms of TB face high direct and indirect costs for diagnosis and treatment [10–13], and these costs are usually higher for patients with confirmed TB than presumptive cases [3,14].

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 [4,15]. 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 [14].

A national TB prevalence survey indicated that the case detection rate of TB was below 50% [16]. This result may not only be due to the complexity but also the high cost of care [15,17,18]. 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 [9,19,20].

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 [21]. Costs for presumptive cases are not well understood, especially in sub-Saharan Africa [3,22]. In addition to financial costs, sociocultural and gender-related factors can shape how patients seek healthcare [23], yet such studies of the influence of these factors are scarce [24]. Finally, only few studies have examined pathways and costs of seeking health care by comparing confirmed and presumptive TB patients [3,10,25].

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.

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 [4]. The district is densely populated with a population of 1,369,000 persons [26]. 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 [27]. 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 [28]. 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 [29].

We included adult, sputum smear-positive TB patients and presumptive TB cases who were consecutively enrolled in the TB-DAR study [4,30] between August 2016 and January 2017, until the target sample size of 100 patients in each category was reached (Figure 1). Based on power calculation and previous studies [3,25] 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.

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 [31].

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 [32]. 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 [32]. 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 [33]. 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 [33]. Diagnostic delay was defined according to the framework of WHO (29) and used in previous studies [34,35] 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 [4]. 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 [36].

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 [4]. 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 [26]. 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 [37,38]. 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 [3,14]. 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).

Patient involvement

Patients were not involved in the development, design, and analysis of this study.

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.

Availability of data and materials

According to the Institutional Review Board of the Ifakara Health Institute, we are not allowed to make the data publicly available. Interested researchers should contact the corresponding author.

Competing interest

All authors declare that they have no competing interests.

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 weeks.

Pathways to care

The spatial distribution of healthcare facilities in the study area show pharmacies and dispensaries are distributed over the whole area Figure (2A). Hospitals are situated mainly in the urban centres and traditional healers predominantly in the peripheral area. Figures (2B) and (2C) 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.

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 3). 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 patients indicated a fourth and fifth visit).

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]).

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.

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]).

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.

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 4). 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).

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 [39], and partially explains the diagnostic delay. Compared to findings of other studies [19,40] 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 [41]. 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 [35,42,43]. 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 [42].

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 [13], and expenditures for seeking healthcare for TB can cause or exacerbate poverty [44]. 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 [13]

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 [44]. 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 [11]. 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.

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 [39]. 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 [45]. These interventions are central for reaching the ambitious WHO targets of zero deaths, disease, and suffering due to TB by 2035 [46].

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Author contributions

Conceived and designed the study: GM, JH, FM, KS, PM, SG, KR, KH, TM, MGW, EZ, and LF. GM, JH, KD, YM and FM analysed the data. GM and LF prepared the first draft of the manuscript. KR, KS, PM, YM, TM, MGW, EM, EZ and LF contributed to the major revision of the manuscript. All authors contributed to final manuscript revisions and approved the final version.

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FIGURE LEGENDS

Figure 1. Flowchart of the study population. Participants were enrolled until the final target of 100 confirmed and 100 presumptive TB patients was reached.

Figure 2. 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.

Figure 3. Spine plots showing distribution of health care facility visits during the pathway of care (first, second, third and fourth/fifth visit) in confirmed and presumptive patients. Numbers on the graph indicate absolute numbers.

Figure 4. 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).

Tables and Figures

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

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.

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

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

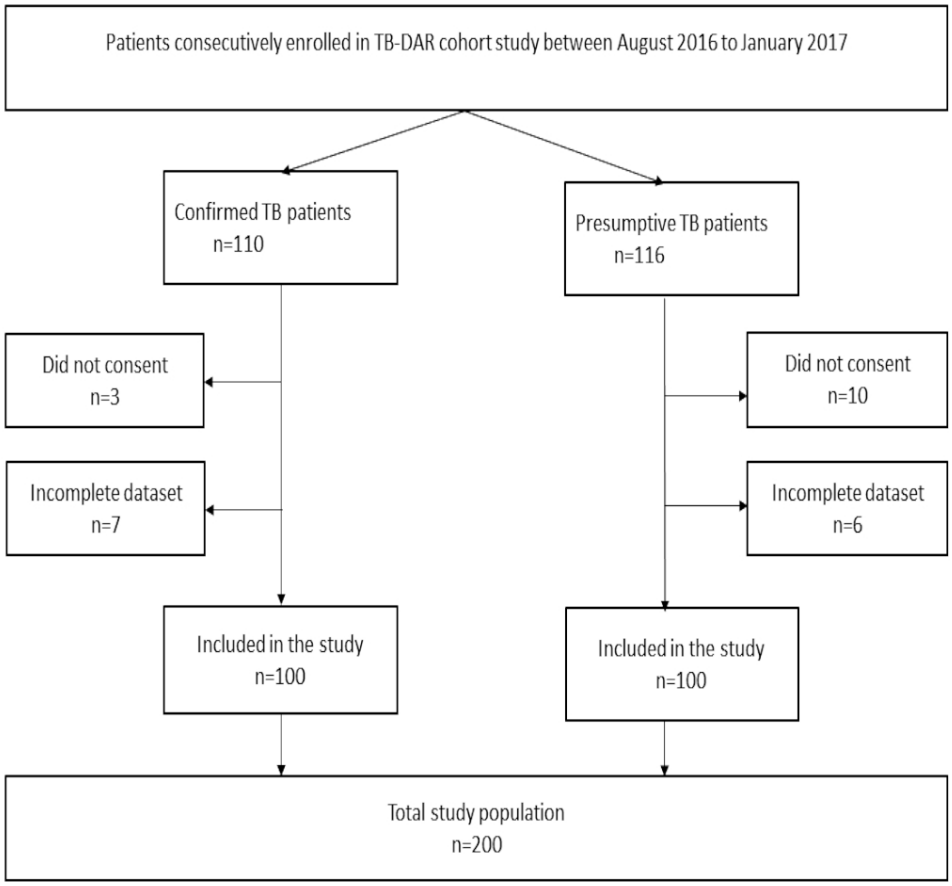
Table 5. Estimates of effects of different factors on median direct, indirect and total costs in USD among confirmed and presumptive TB patients

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 education



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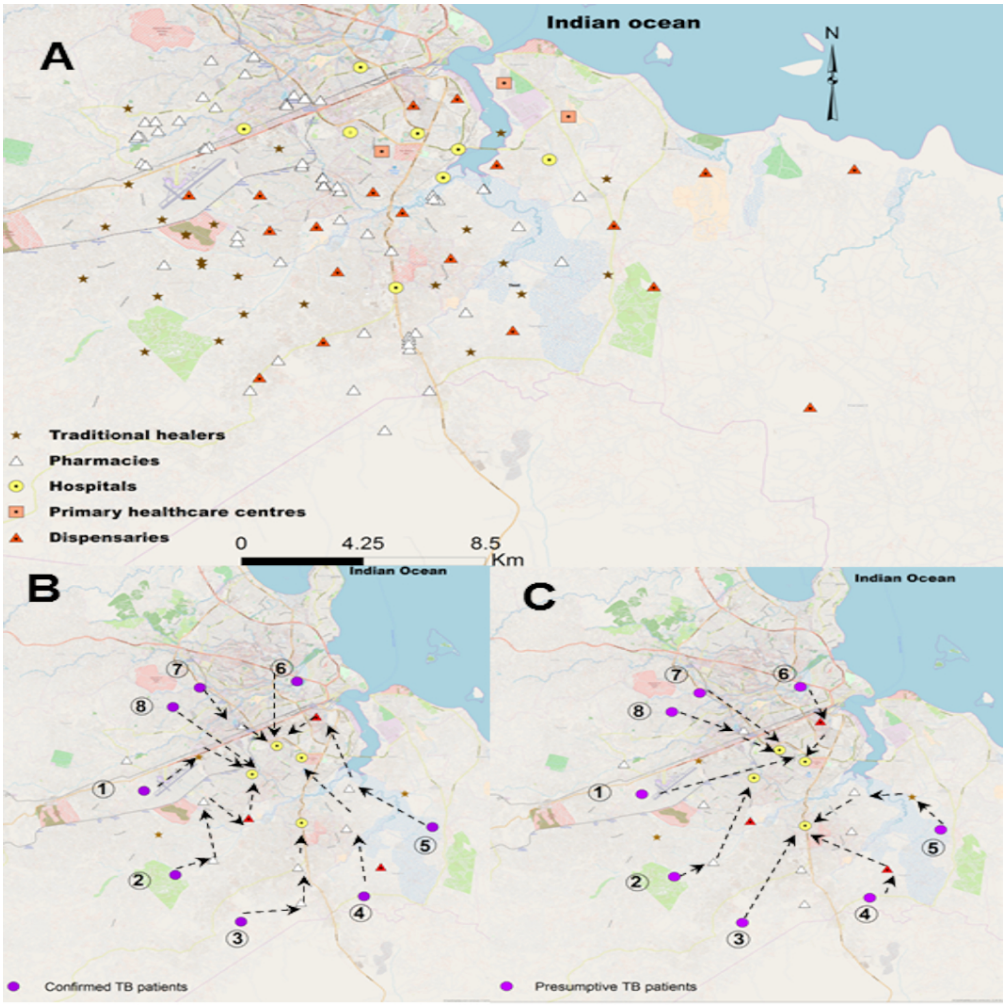

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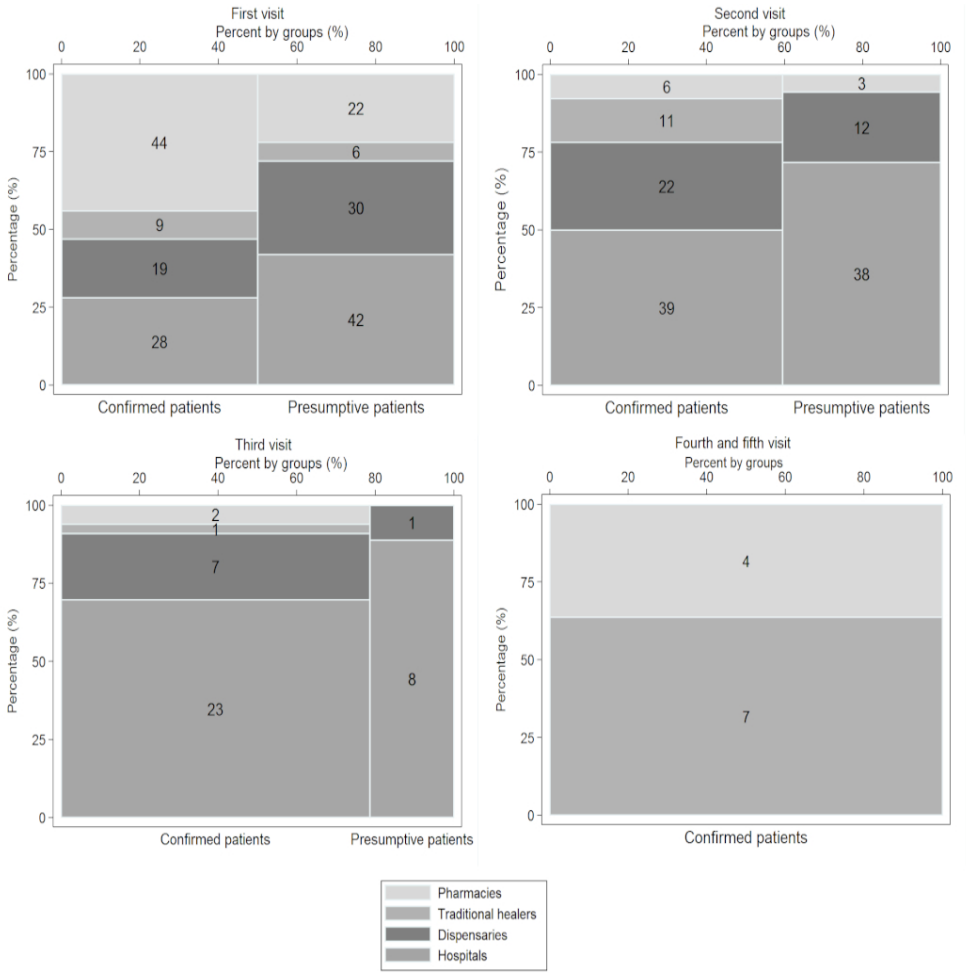

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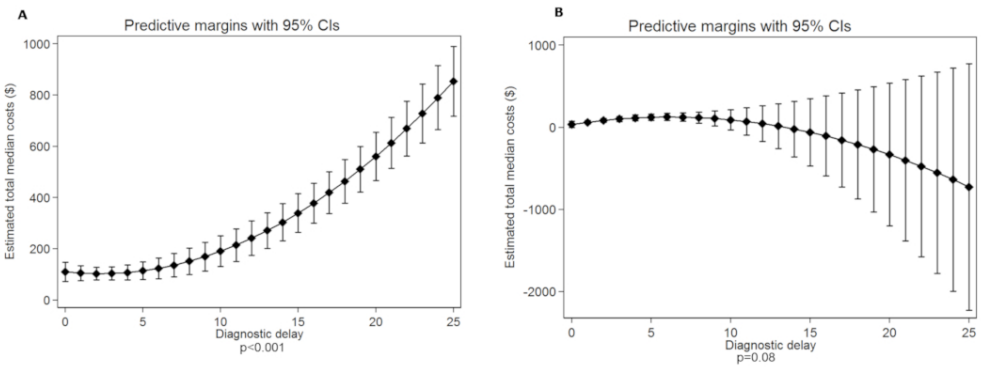

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Supplementary Table 1. Direct costs associated with first, second and >2 visits for patients with confirmed and presumptive TB.

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.

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 6
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 6
Methods			
Study design	4	Present key elements of study design early in the paper	Page 7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	Page 7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 7-8
Bias	9	Describe any efforts to address potential sources of bias	Page 9
Study size	10	Explain how the study size was arrived at	Page 7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 9
		(*b*) Describe any methods used to examine subgroups and interactions	Page 9
		(*c*) Explain how missing data were addressed	-
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	-
		(*e*) Describe any sensitivity analyses	-
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Page 12
		(b) Give reasons for non-participation at each stage	-
		(c) Consider use of a flow diagram	Page 7
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	
		(b) Indicate number of participants with missing data for each variable of interest	-
Outcome data	15*	Report numbers of outcome events or summary measures	Page 13
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	-
		(*b*) Report category boundaries when continuous variables were categorized	-
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Page 14
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 17
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 20
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 17-20
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 17-20
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 22

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Pathways and associated costs of care in confirmed and presumptive tuberculosis patients in Tanzania: A cross-sectional study

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TITLE PAGE:

Pathways and associated costs of care in confirmed and presumptive tuberculosis patients in Tanzania: A cross-sectional study

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4 figures and 5 tables, Supplementary File (3 tables)

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. 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 healthcare utilization.

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.

BACKGROUND

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 [1,2]. Many patients consult various healthcare providers before being diagnosed with TB [3,4]. These pathways are usually complex and delayed diagnosis and treatment may increase morbidity and mortality [5]. 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 [6]. 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 [7,8]. 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 [9]. However, patients with symptoms of TB face high direct and indirect costs for diagnosis and treatment [10–13], and these costs are usually higher for patients with confirmed TB than presumptive cases [3,14].

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 [4,15]. The complex pathways to care may begin at pharmacies and basic healthcare facilities with no TB diagnostics before reaching healthcare facilities with TB diagnostic capacity [14].

A national TB prevalence survey indicated that the case detection rate of TB was below 50% [16]. This result may not only be due to the complexity but also the high cost of care [15,17,18]. 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 [9,19,20].

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 [21]. Costs for presumptive cases are not well understood, especially in sub-Saharan Africa [3,22]. In addition to financial costs, sociocultural and gender-related factors can shape how patients seek healthcare [23], yet such studies of the influence of these factors are scarce [24]. Finally, only few studies have examined pathways and costs of seeking healthcare by comparing confirmed and presumptive TB patients [3,10,25].

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.

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 [4]. The district is densely populated with a population of 1,369,000 persons [26]. 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 [27]. 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 [28]. 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 [29].

We included adult, sputum smear-positive TB patients and presumptive TB cases who were consecutively enrolled in the TB-DAR study [4,30] between August 2016 and January 2017, until the target sample size of 100 patients in each category was reached (Figure 1). Based on power calculation and previous studies [3,25] 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.

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 [31].

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 [32]. 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 [32]. 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 [33]. 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 [33]. Diagnostic delay was defined according to the framework of WHO (29) and used in previous studies [34,35] 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 [4]. 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 [36].

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 [4]. 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 [26]. 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 [37,38]. 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 [3,14]. 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). All maps were obtained from Open Street Maps.

Patient involvement

Patients were not involved in the development, design, and analysis of this study.

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.

Availability of data and materials

According to the Institutional Review Board of the Ifakara Health Institute, we are not allowed to make the data publicly available. Interested researchers should contact the corresponding author.

Competing interest

All authors declare that they have no competing interests.

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 weeks.

Pathways to care

The spatial distribution of healthcare facilities in the study area show pharmacies and dispensaries are distributed over the whole area Figure (2A). Hospitals are situated mainly in the urban centres and traditional healers predominantly in the peripheral area.

Figures (2B) and (2C) 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.

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 3). 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 patients indicated a fourth and fifth visit).

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]).

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.

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]).

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.

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 4). 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).

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 [39], and partially explains the diagnostic delay. Compared to findings of other studies [19,40] 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 [41]. 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 [35,42,43]. 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 [42].

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 [13], and expenditures for seeking healthcare for TB can cause or exacerbate poverty [44]. 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 [13]

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 [44]. 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 [11]. 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.

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.

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 healthcare utilization [39]. Reducing the direct and indirect costs associated with treatment seeking is likely to support confirmed and presumptive TB patients in timely accessing healthcare 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 [45]. These interventions are central for reaching the ambitious WHO targets of zero deaths, disease, and suffering due to TB by 2035 [46].

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Author contributions

Conceived and designed the study: GM, JH, FM, KS, PM, SG, KR, KH, TM, MGW, EZ, and LF. GM, JH, KD, CS, YPM and FM analysed the data. GM and LF prepared the first draft of the manuscript. KR, KS, PM, YPM, TM, MGW, EM, EZ, CS and LF contributed to the major revision of the manuscript. All authors contributed to final manuscript revisions and approved the final version.

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FIGURE LEGENDS

Figure 1. Flowchart of the study population. Participants were enrolled until the final target of 100 confirmed and 100 presumptive TB patients was reached.

Figure 2. 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.

Figure 3. Spine plots showing distribution of health care facility visits during the pathway of care (first, second, third and fourth/fifth visit) in confirmed and presumptive patients. Numbers on the graph indicate absolute numbers.

Figure 4. 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).

Tables and Figures

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

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 (37.1-161.4)	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.

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

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

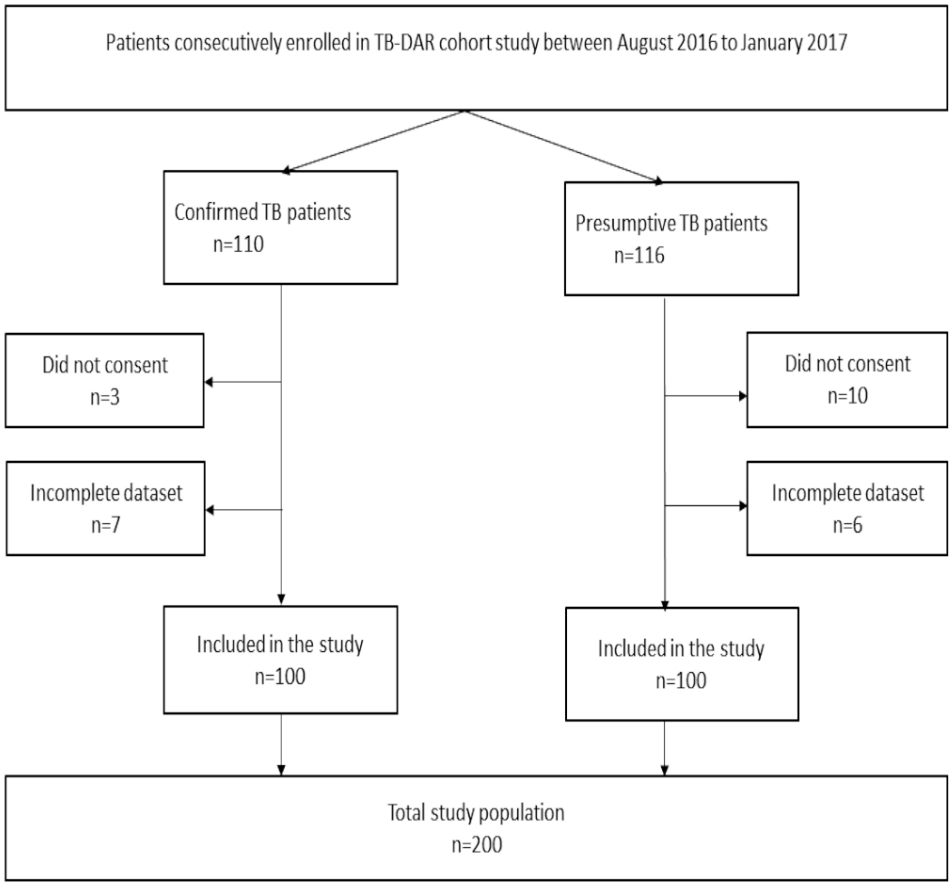
Table 5. Estimates of effects of different factors on median direct, indirect and total costs in USD among confirmed and presumptive TB patients

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 education



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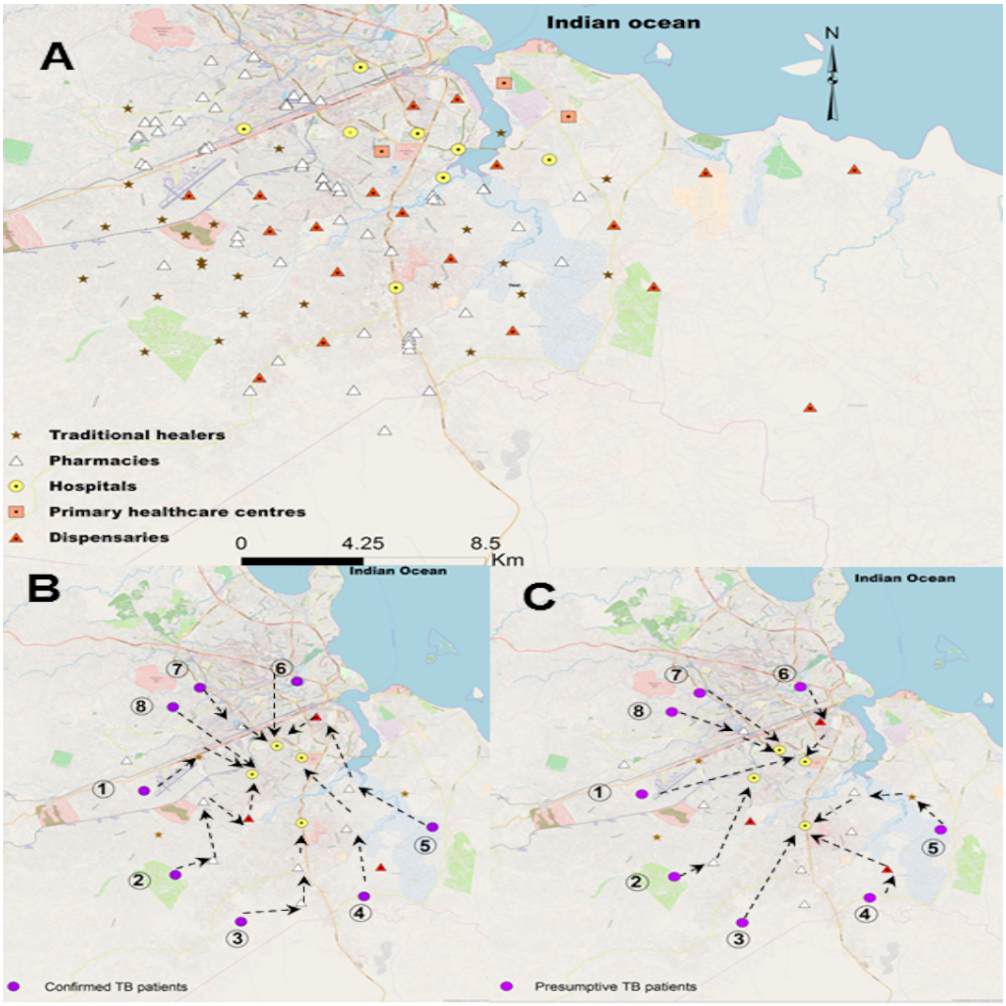

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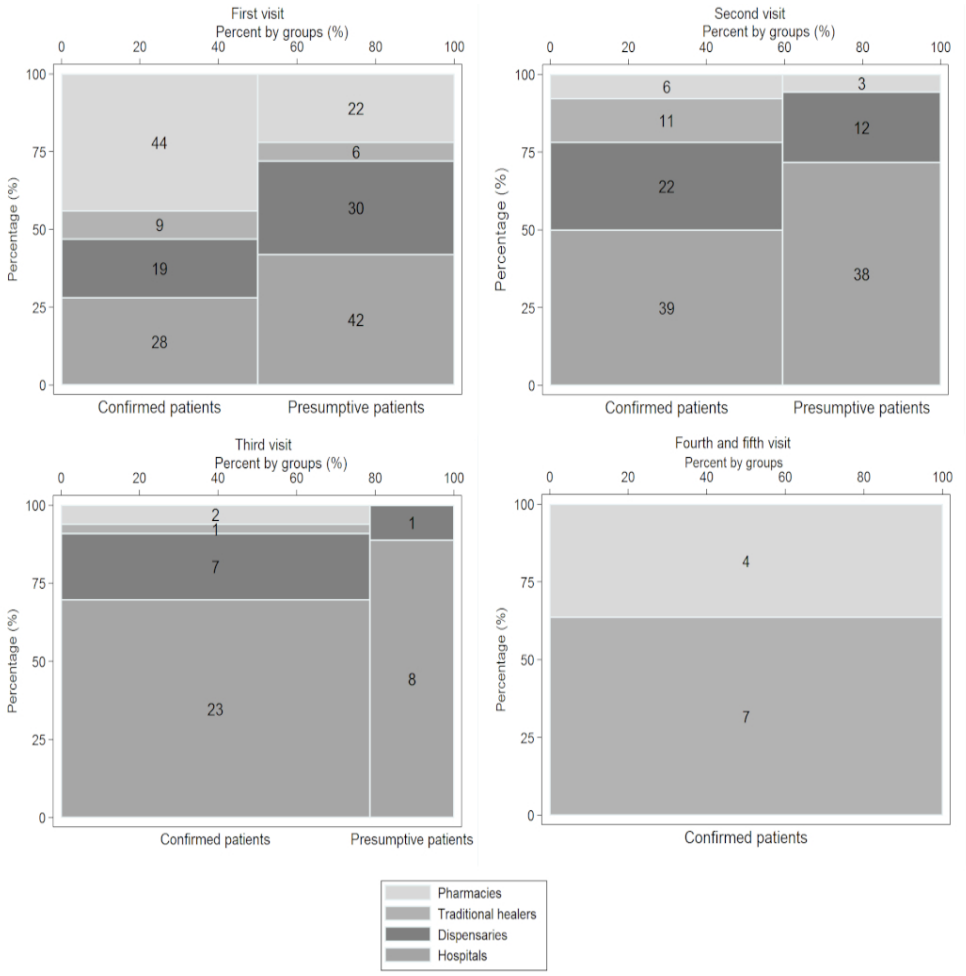

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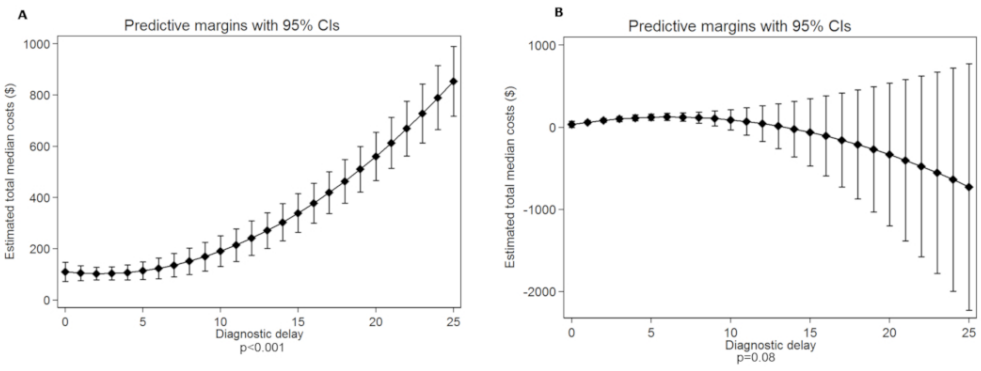

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Supplementary Table 1. Direct costs associated with first, second and >2 visits for patients with confirmed and presumptive TB.

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
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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 6
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 6
Methods			
Study design	4	Present key elements of study design early in the paper	Page 7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	Page 7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 7-8
Bias	9	Describe any efforts to address potential sources of bias	Page 9
Study size	10	Explain how the study size was arrived at	Page 7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 9
		(*b*) Describe any methods used to examine subgroups and interactions	Page 9
		(*c*) Explain how missing data were addressed	-
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	-
		(*e*) Describe any sensitivity analyses	-
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Page 12
		(b) Give reasons for non-participation at each stage	-
		(c) Consider use of a flow diagram	Page 7
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	
		(b) Indicate number of participants with missing data for each variable of interest	-
Outcome data	15*	Report numbers of outcome events or summary measures	Page 13
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	-
		(*b*) Report category boundaries when continuous variables were categorized	-
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Page 14
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 17
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 20
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 17-20
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 17-20
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 22

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.