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Tuberculosis-related knowledge is associated with patient outcomes in shantytown residents; results from a cohort study, Peru

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Summary *Objectives:* Tuberculosis is frequent among poor and marginalized people whose limited tuberculosis-related knowledge may impair healthcare access. We characterised tuberculosis-related knowledge and associations with delayed treatment and treatment outcome.
Methods: Tuberculosis patients (n = 943), people being tested for suspected tuberculosis (n = 2020), and randomly selected healthy controls (n = 476) in 16 periurban shantytowns were interviewed characterizing: socio-demographic factors; tuberculosis risk-factors; and patients' treatment delay. Principle component analysis was used to generate a tuberculosis-related knowledge score. Patients were followed-up for median 7.7 years. Factors associated with tuberculosis treatment delay, treatment outcome and tuberculosis recurrence were assessed using linear, logistic and Cox regression.
Results: Tuberculosis-related knowledge was poor, especially in older people who had not completed schooling and had never been diagnosed with tuberculosis. Tuberculosis treatment delay was median 60 days and was more delayed for patients who were poorer, older, had more severe tuberculosis and in only unadjusted analysis with incomplete schooling and

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low tuberculosis-related knowledge (all $p \leq 0.03$). Lower than median tuberculosis-related knowledge was associated with tuberculosis recurrence (unadjusted hazard ratio = 2.1, $p = 0.008$), and this association was independent of co-morbidities, disease severity and demographic factors (multiple regression adjusted hazard ratio = 2.6, $p = 0.008$).
Conclusions: Low tuberculosis-related knowledge independently predicted tuberculosis recurrence. Thus health education may improve tuberculosis prognosis.

Introduction

Tuberculosis (TB) was estimated to kill 1.5 million people in 2013.[1] The connection between poverty and TB is well established; poverty increases TB risk and poverty may be worsened by TB-associated direct and indirect costs.[2] Socioeconomic determinants other than economic poverty such as lack of TB-related knowledge, incomplete schooling, stigma and marginalisation may also increase TB risk but these associations are poorly characterised.[3]

Lack of knowledge and erroneous beliefs about TB are common amongst TB patients,[4,5] and have been associated with older age,[6] incomplete schooling and unemployment.[5] TB-related knowledge has been associated with delayed treatment but data are contradictory.[7,8] Delayed treatment may adversely affect outcomes but associations of TB-related knowledge with health outcomes are not well characterised.

Associations between socioeconomic factors (including TB-related knowledge), delayed diagnosis and treatment outcomes are important because of the increasing consensus that socioeconomic support should be included in TB control interventions.[9–11] Indeed, ecological analyses have demonstrated that global TB rates are strongly associated with poverty and changes in TB rates are principally associated with changes in socioeconomic development, not biomedical factors.[12,13] Furthermore, socioeconomic interventions may strengthen TB control and have recently been included in TB control priorities by the World Health Organization.[14]

Despite increasing interest in socioeconomic aspects of TB, the importance of TB-related knowledge as a potential social determinant of TB has been the subject of little research. Our objective was to address this knowledge gap by characterising TB-related knowledge and testing for associations with TB treatment delay and clinical outcomes. We also collected data concerning current and potential future sources of TB-related knowledge and health promotion.

In resource-constrained settings, TB treatment outcome assessed at the time of treatment completion is unreliable because cure is usually assessed using insensitive sputum microscopy.[15,16] Consequently, inadequate therapy may cause transient disease suppression manifest as apparent cure followed by TB recurrence. Thus our assessment of clinical outcomes included both apparent cure at the time of treatment completion and also post-treatment follow-up for TB recurrence.

We hypothesized that knowledge about TB would be poor and that those with least TB-related knowledge would be prone to delayed treatment and adverse clinical outcomes.

Methods

Ethics statement

The study was done with the approval of and in collaboration with the Peruvian ministry of health and also had approval from the internationally accredited ethics committee of Universidad Peruana Cayetano Heredia. All participants gave informed written consent.

Study design

This was a descriptive observational study of baseline data in: 1. TB patients; 2. people with suspected TB; and 3. healthy controls. This was followed by a prospective cohort study of only TB patients.

Setting

The study took place in 16 periurban contiguous shantytowns in Ventanilla, Peru. This region has a registered population of 277,895 people, an annual TB case-notification rate of 162 cases per 100,000 people and frequent poverty (32% of people live on $\leq$US$1/day).[3]

Population

Three groups were surveyed to characterise socioeconomic TB risk factors: 1. patients diagnosed by the TB program with laboratory-proven pulmonary TB were invited to participate from 2003 to 2007; 2. people with suspected TB (either because they attended selected health posts and had a productive cough for more than 2 weeks, or because they lived with a newly diagnosed TB patient), but were not known to have TB disease were invited to participate concurrently from 2003 to 2007; 3. control households from the same region were selected from a satellite map using random number tables and were invited to participate from 2006 to 2007. Then patients were followed-up until late 2013. To reduce bias, all consecutive: 1. patients; 2. people with suspected TB; and 3. all members of the healthy control households in the study region throughout these periods were assessed for eligibility and invited to participate. Inclusion criteria for all participants included age $\geq$15 years.

Population characteristics

Initially, questionnaires were refined with 125 consecutive pilot participants and their data were excluded from

analysis. All participants were visited by a research nurse in their homes and completed questionnaires characterising socio-demographic data, schooling, TB-related knowledge, and TB severity. TB risk factors that were characterised included self-reported diagnosis of any other respiratory diseases, diabetes, and smoking any cigarette in the week before the interview. All participants were asked if they had been diagnosed with TB disease previously. Height and weight were measured and low body mass index was considered an indicator of severe disease.

Co-morbidities

HIV testing was recommended and offered free of charge to all patients by the national TB program. However, HIV only infects $<$0.5% of adults and $<$3% of TB patients in this population,[17] so patients who declined testing were classified as having no evidence of HIV infection.

Poverty score

Principle component analysis was used to generate a weighted composite index of chronic poverty from survey questions concerning education, services and housing, as described,[3] for which 5.5% missing data were imputed. Income was not included in the chronic poverty index because income may be rapidly reduced by TB disease.[2,18]

Laboratory data

All participants with cough were asked for a sputum sample that was tested with microscopy, solid[19] and liquid culture with direct[20] and indirect drug-susceptibility testing.[21] Strongly positive Ziehl-Neelsen sputum microscopy grade was used as an indicator of disease severity defined as '++' or '+++' (versus less severe disease defined as '+', borderline or negative).[19]

TB-related knowledge

The TB-related knowledge questionnaire constituted 12 questions that were based upon previous studies.[8,22,23] Principal component analysis was used to generate a TB-related knowledge score for which non-contributory questions were excluded. The score was the first principal component.

Access to media sources

Access to media sources that may be used for health promotion was assessed by questions regarding sources of TB-related knowledge and access to television, radio and telephones.

TB beliefs

TB beliefs and attitudes regarding TB were assessed by questionnaire.

Treatment delay

Treatment delay was measured from the first day of any clinically relevant symptoms that the patient attributed to TB until the date of the recruitment interview when the patient was starting treatment.

Early-treatment outcome

According to Peruvian policy, TB patients were considered to have defaulted if they missed $>$30 consecutive days treatment; and treatment failure was defined by 4 positive monthly sputum microscopy results or 2 consecutive positive results after 2 consecutive negative results. Patients who completed therapy without default or treatment failure were classified as cured.

TB recurrence

We collaborated with the TB program in surveillance for all new TB diagnoses in this region to prospectively identify TB recurrences in participants. We also revisited patients every 3 years to check whether they had required TB re-treatment for TB recurrence. Whenever possible re-treatment was confirmed with TB program records. Surveillance and active follow-up took place continuously until mid-2013.

Analysis

All analyses were performed using STATA (StataCorp version 12) and all p-values were 2-sided. Continuous variables with non-Gaussian distributions were summarised as medians and inter-quartile ranges (IQR) and divided into dichotomous variables (high versus low values) by the median value. Dichotomous variables were summarised as proportions and compared with logistic regression to determine odds ratios (OR). In all regression analyses, independence of associations with TB-related knowledge was assessed by inclusion of variables that were considered to be potentially confounding variables based upon our experiences of TB epidemiology in this region and upon the published literature. For the analyses adjusted by multiple regression, non-contributory variables were removed stepwise according to the likelihood ratio test. Treatment delay data were logarithm (base-10) transformed to make their distribution approximately Gaussian for linear regression analysis. Recurrence data were analysed using Cox regression time-to-event analysis to calculate hazard ratios (HR) that included all available data. Recurrence data were illustrated with Kaplan—Meier curves until less then one-third of the population had follow-up data.[24]

Study power

The sample size was opportunistic. Power calculations demonstrated that the study had 80% power at the 95% significance level to detect an effect of low TB-related knowledge of 5% on TB treatment delay, 32% on adverse early treatment outcome and 52% on TB recurrence.[25]

Sensitivity analyses

1. Time to recurrence data were also analysed considering only early follow-up in case TB-related knowledge was differentially associated with early versus late TB recurrence. 2. Healthy controls were recruited only for the last part of the study, not concurrently with the entire recruitment period for TB patients and people with suspected TB, so a sensitivity analysis compared all of the control data with data collected only during the last 2 years of recruitment.

Results

Of the 3701 people invited to participate, 98% (3631) consented. For the research after the completion of the pilot phase, 3506 participants were recruited and 98% (3439/3506) provided complete TB-related knowledge questionnaire data so constituted the study population: 943 TB patients; 2020 people with suspected TB; and 476 healthy controls (Fig. 1).

The study population and their characteristics are shown in Table 1. People with suspected TB and healthy controls were older than TB patients and more likely to be female (both $p < 0.001$). TB patients had lower body mass index than other groups ($p < 0.001$), 19% had TB previously, 60% were males and patient median age was 27 years. Patients had significantly greater chronic poverty than people with suspected TB and healthy controls ($p \leq 0.004$) and 56% of patients had not completed secondary school. Among TB patients, TB sputum microscopy grade was strongly positive for 65% and multi-drug resistant (MDR)-TB was diagnosed in 12%.

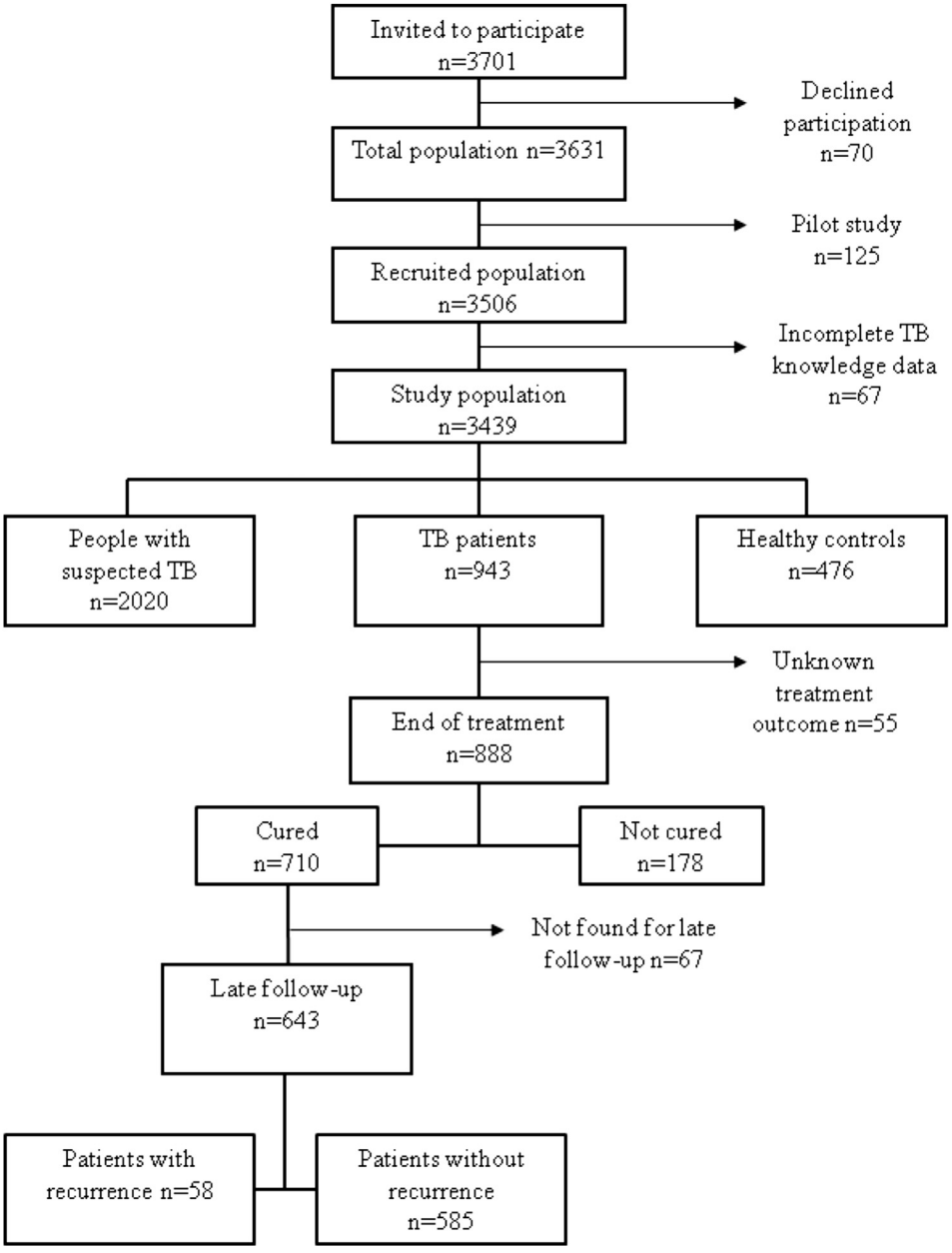

Figure 1 Study flow chart.

Table 1 Characteristics of study participants.

Characteristic	TB patients (n = 943)	Suspected TB (n = 2020)	Healthy controls (n = 476)	p[a] Patients versus suspected TB	Patients versus controls	Suspected TB versus controls
Low TB-related knowledge score; % (n/N) below patient median	50% (472/943)	64% (1294/2020)	83% (394/476)	<0.001	<0.001	<0.001
TB-related knowledge score; median (IQR)[b]	0.063 (−0.77–1.1)	−0.33 (−1.2–0.43)	−0.78 (−1.7–−0.012)	<0.001	<0.001	<0.001
Socio-demographic factors						
Male sex; % (n/N)	60% (566/943)	40% (811/2020)	37% (176/476)	<0.001	<0.001	0.2
Age; % (n/N) above patient median	49% (461/943)	56% (1138/2020)	60% (285/476)	<0.001	<0.001	0.2
Age; median (IQR)[b]	27 (21–37)	30 (22–43)	32 (22–43)	<0.001	<0.001	0.5
Did not complete secondary school; % (n/N)	56% (529/943)	57% (1145/2019)	54% (256/476)	0.6	0.2	0.2
Chronic poverty; % (n/N) below patient median	50% (473/943)	45% (902/2020)	41% (196/476)	0.004	0.001	0.2
Chronic poverty; median (IQR)[b]	−0.11 (−1.5–1.4)	0.12 (−1.2–1.6)	0.26 (−0.89–1.3)	<0.001	0.001	0.5
TB risk factors						
Past TB; % (n/N)	19% (174/939)	12% (235/2015)	5.5% (26/474)	<0.001	<0.001	<0.001
Body mass index; % (n/N) below patient median	50% (450/900)	20% (400/1970)	11% (51/471)	<0.001	<0.001	<0.001
Body mass index; median (IQR)[b]	21 (19–23)	24 (22–28)	25 (23–29)	<0.001	<0.001	<0.001
TB disease severity						
Multi-drug resistance; % (n/N)	12% (102/854)	NA	NA	NA	NA	NA
Microscopy grade strongly positive; % (n/N)	65% (610/943)	NA	NA	NA	NA	NA
Treatment delay in days; median (IQR)	60 (30–99)	NA	NA	NA	NA	NA
Outcomes						
Early outcome: Cured; % (n/N)	80% (710/888)	NA	NA	NA	NA	NA
Early outcome: Death; % (n/N)	1.9% (17/888)	NA	NA	NA	NA	NA
Early outcome: Treatment failure; % (n/N)	6.0% (53/888)	NA	NA	NA	NA	NA
Early outcome: Treatment default; % (n/N)	12% (108/888)	NA	NA	NA	NA	NA
TB recurrence; % (n/N)	9.0% (58/643)	NA	NA	NA	NA	NA
Coexisting diseases						
HIV (suspected or confirmed); % (n/N)	1.8% (15/833)	NA	NA	NA	NA	NA
Diabetes (self-reported); % (n/N)	2.2% (21/943)	NA	NA	NA	NA	NA
Other respiratory diseases (self-reported); % (n/N)	6.8% (64/938)	NA	NA	NA	NA	NA
Smoking any cigarette in the week before the interview; % (n/N)[c]	3.0% (28/943)	NA	NA	NA	NA	NA

Abbreviations: n = number; N = sample size; NA = not applicable; IQR = inter-quartile range.

[a] Male people with suspected TB and healthy-controls had limited availability because they were often away working, so these groups under-represented males relative to 50% males in the general population. All statistical comparisons in Table 1 were therefore adjusted for gender.

[b] For these p values, the continuous data were compared.

[c] This question was left blank by 39% (373/973) patients, which we analysed as implying that they had not smoked during this period.

Principle component analysis indicated that TB patients' TB-related knowledge was best summarized by 7 questions that therefore constituted the TB-related knowledge, which weighted questions about constitutional TB symptoms (night sweats and fevers) most strongly (Table 2). TB-related knowledge was poor e.g. less than half of participants knew that night sweats or fevers were TB symptoms, although 75% and 70% of TB patients reported these symptoms, respectively.

Access to media sources of TB-related knowledge are shown in Table 2. For TB patients, 43% stated that they first heard about TB from family or friends and only 4.7% reported TV or radio to be their primary TB-related knowledge source, although almost all owned a functioning television or radio. Living in a house with a functioning telephone (fixed and/or mobile) was uncommon and was less common for patients (42%) than healthy controls (64%, $p < 0.001$).

Analysing data for all participants together, higher TB-related knowledge was associated with current TB, female sex, complete schooling and previous TB (Table 3). When analysing data only for TB patients, TB-related knowledge was associated with younger age, complete schooling and low body mass index (Table 3). Low TB-related knowledge was associated with having social networks (family and friends) as the primary source of TB-related knowledge (OR = 1.4, $p = 0.02$, data not shown).

Details of self-reported TB beliefs are shown in Supplementary Table 1. Amongst TB patients: 66% thought that the best way to prevent TB infection was eating better whereas avoiding TB exposure was the answer given by 11%; and 71% thought that religion would help them to overcome TB. Most participants thought that using separate food utensils would prevent TB contagion.

The delay from symptom onset to the recruitment interview at the time of treatment initiation was median 60 (IQR 30—99) days and was longer for patients with low TB-related knowledge (unadjusted $p = 0.02$), principally because some of them had very prolonged treatment delay (Fig. 2). Treatment delay was significantly associated with older age, chronic poverty, low body mass index, strongly-positive sputum microscopy and in only unadjusted analysis with incomplete schooling and low TB-related knowledge (Table 4). Analysis adjusted by multiple regression for potentially confounding variables demonstrated that the association between low TB-related knowledge and prolonged treatment delay in unadjusted analysis was independent of disease severity but this association was not independent of and was therefore explained by patient poverty and demographics (Table 4).

Data assessing early-treatment outcome at the time of treatment completion were available for 94% (888/943) patients and were characterized by the TB program as 80% cured, 12% defaulted from treatment, 1.9% died and 6.0% treatment failed. Adverse treatment outcome (death during treatment, treatment failure or default) was independently associated in adjusted multiple logistic regression with not having completed secondary school (OR = 1.6, $p = 0.01$), previous TB (OR = 3.7, $p < 0.001$) and MDR-TB (OR = 4.6, $p < 0.001$). TB-related knowledge was not associated with adverse early-treatment outcome (OR = 0.9, $p = 0.8$).

TB recurrence was assessed in patients who had initially been categorised as cured, so excluded patients who had not

Table 2 TB-related knowledge questionnaire results, sources of TB-related knowledge and access to potential media campaigns.

Question	Vector[a]	% (n/N) correct		
		Patients	Suspected TB	Healthy controls
TB-related knowledge[b]				
Are night sweats a symptom of TB?	0.54	49% (459/943)	34% (678/2020)	16% (75/476)
Is fever a symptom of TB?	0.42	52% (486/943)	41% (829/2020)	22% (103/476)
Is cough a symptom of TB?	0.37	87% (821/943)	85% (1713/2020)	75% (359/476)
Is weight loss a symptom of TB?	0.37	60% (568/943)	60% (1205/2020)	45% (215/476)
Is TB cough infectious?	0.31	91% (862/943)	91% (1841/2020)	89% (424/476)
Is fatigue a symptom of TB?	0.31	59% (554/943)	43% (862/2020)	31% (148/476)
What is most important to do to get better from TB?	0.25	77% (724/943)	73% (1484/2020)	81% (384/476)
Source of TB-related knowledge: where participants heard about TB for the first time				
Friends/family		43% (402/942)	45% (918/2018)	32% (153/476)
School		28% (262/942)	29% (577/2018)	29% (139/476)
Television/radio		4.7% (44/942)	4.2% (84/2018)	6.3% (30/476)
Other		25% (234/942)	22% (439/2018)	32% (154/476)
Access to potential media campaigns to increase TB-related knowledge				
Live in house with functioning television		89% (840/943)	92% (1856/2018)	95% (452/475)
Live in house with functioning radio		80% (754/943)	83% (1675/2018)	77% (365/472)
Live in house with functioning telephone		42% (399/942)	44% (896/2017)	64% (303/475)

Abbreviations: n = number; N = sample size.

[a] Vector indicates the principal component analysis factor loading for the contribution that each variable makes to the composite TB-related knowledge score.

[b] Questions concerning TB associations with pallor, haemoptysis, chest pain, headache and prevention of TB transmission did not significantly contribute to the weighted TB-related knowledge score and were therefore not included.

Table 3 Associations with below-median TB-related knowledge score analysed as the outcome (dependent) variable in logistic regression for all participants (healthy controls, people with suspected TB and TB patients) and also analysed only for TB patients.

	All participants				TB patients			
	Unadjusted regression		Adjusted regression		Unadjusted regression		Adjusted regression	
	n = 3439		n = 3317		n = 943		n = 900	
	Odds ratio	p	Odds ratio	p	Odds ratio	p	Odds ratio	p
TB suspect versus TB patients	1.8	<0.001	1.9	<0.001	NA	NA	NA	NA
Healthy controls versus TB patients	4.8	<0.001	5.4	<0.001	NA	NA	NA	NA
Demographic factors								
Age (above patient median)	1.1	0.07			2.3	<0.001	2.3	<0.001
Male sex	1.3	0.001	1.7	<0.001	0.96	0.8		
Did not complete secondary school	1.7	<0.001	1.9	<0.001	2.1	<0.001	1.9	<0.001
Chronic poverty (wealth index below patient median)	1.2	0.003			1.7	<0.001		
TB disease severity								
Past TB	0.51	<0.001	0.54	<0.001	0.80	0.2		
Multi-drug resistant TB	NA	NA	NA	NA	0.72	0.1		
Body mass index (below patient median)	0.79	0.003			0.63	0.001	0.69	0.008
TB microscopy grade strongly positive	NA	NA	NA	NA	1.1	0.5		

Abbreviations: n = number; NA = not applicable.

completed TB treatment. Considering these 710 cured patients, 91% (n = 643) had long-term follow-up data for a median duration of 7.7 years (IQR 6.5–8.7), which identified TB recurrence in 9.0% (58/643). In unadjusted analysis, TB recurrence was significantly associated with low TB-related knowledge (HR = 2.1, p = 0.008, Table 5). In forward stepwise multiple regression analysis this statistical significance was maintained when adjusted for: i. sex, MDR-TB, HIV and smoking; ii. plus other respiratory diseases; iii. plus age and body mass index, treatment delay, and diabetes; and iv. plus incomplete schooling, chronic poverty, past TB, and strongly positive microscopy grade (all HR $\geq$ 2.3, p $\leq$ 0.009, Table 5). In a post-hoc sub-group analysis, low TB-related knowledge was associated with TB recurrence when considering only

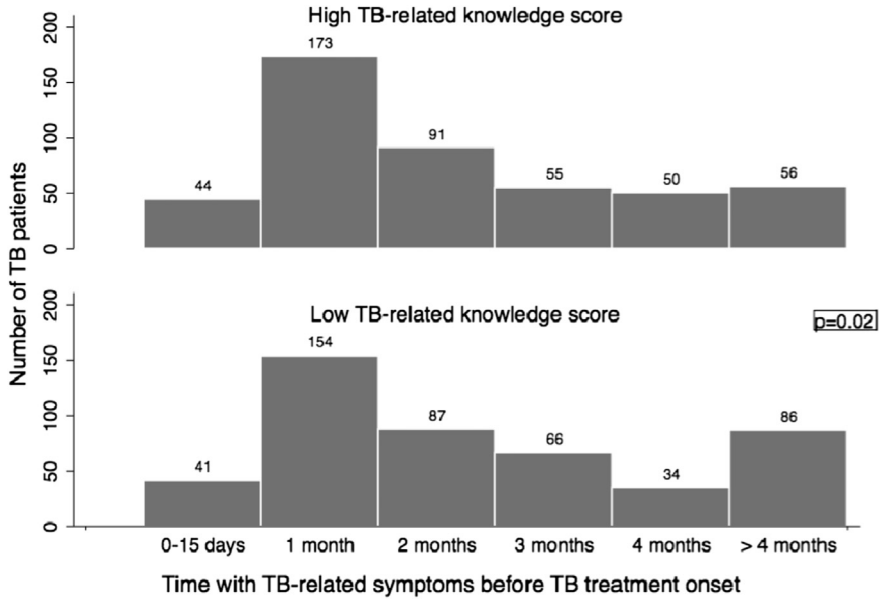

Figure 2 Histogram of TB patient treatment delay (measured from symptom onset until treatment initiation). TB patient treatment delay was lower for patients with high versus low TB-related knowledge score (p = 0.02, see Results section). Treatment delay is shown in 6 intervals: within the Peruvian target of 15 days, 1 month (+/−15 days), 2 months (+/−15 days), 3 months (+/−15 days), 4 months (+/−15 days) and more than 4 months. The number above each bar indicates the number of patients.

Table 4 Associations with longer treatment delay. Note that treatment delay data was subjected to logarithmic transformation prior to linear regression analysis (see Methods section).

	Unadjusted linear regression		Linear regression adjusted for disease severity		Linear regression adjusted for demographics & disease severity	
	(n = 937)		(n = 895)		(n = 895)	
	Coefficient	p	Coefficient	p	Coefficient	p
TB-related knowledge score (below patient median)	0.061	0.02	0.065	0.02	0.031	0.3
Demographic factors						
Age; above patient median years	0.11	<0.001			0.11	<0.001
Male sex	−0.028	0.3			−0.060	0.03
Did not complete secondary school	0.080	0.003				
Chronic poverty (wealth index below patient median)	0.10	<0.001			0.094	<0.001
Crowded (above patient median)	−0.044	0.1				
TB disease severity						
Past TB	0.033	0.3				
Multi-drug resistant TB	0.039	0.4				
Body mass index (below patient median)	0.061	0.02	0.067	0.01	0.087	0.001
TB microscopy grade strongly positive	0.070	0.01	0.068	0.02	0.063	0.02

Abbreviations: n = number.

the 535 patients who did not have MDR-TB (HR = 2.1, p = 0.03) and a similar trend was present for the 44 patients with MDR-TB (HR = 3.1, p = 0.06). Fig. 3 shows the Kaplan–Meier curve of the association between TB-related knowledge and TB recurrence, most of which occurred soon after treatment completion.

A sensitivity analysis of the association between low TB-related knowledge and TB recurrence considering only early follow-up gave similar results (Fig. 3 footnote). An additional sensitivity analysis comparing the control data with only approximately concurrent data (from the last 2 years of recruitment of TB patients and people with suspected TB) had very similar results to the above findings (Supplementary Table 2).

Table 5 Associations with TB recurrence in Cox regression analysis.

	Cox regression (n = 643)		
	Hazard ratio	95% CI	p
Unadjusted analysis			
TB-related knowledge score (below patient median)	2.1	1.2–3.6	0.008
***Regression adjusted for*:**			
(i) Sex, MDR-TB, HIV and smoking	2.3	1.2–4.2	0.009
(ii) the variables in (i) plus other respiratory diseases	2.3	1.2–4.2	0.009
(iii) the variables in (ii) plus age, body mass index, treatment delay, and diabetes	2.6	1.3–5.0	0.004
(iv) the variables in (iii) plus incomplete schooling, chronic poverty, past TB, strongly positive TB microscopy grade	2.6	1.3–5.2	0.008

Abbreviations: n = number.

Discussion

This study demonstrated low TB-related knowledge amongst impoverished communities, including people with suspected and proven TB disease. Amongst TB patients, low TB-related knowledge was most common in the elderly and those who had incomplete schooling and this was clinically relevant because low TB-related knowledge independently predicted TB recurrence.

Families and friends were frequent primary sources of TB-related knowledge and these sources were associated with low TB-related knowledge, implying that media campaigns run by the TB program should try to increase health promotion to people at high-risk of becoming TB patients e.g. members of TB-affected households. Television and radio ownership was frequent, suggesting that these may be utilised to increase TB-related knowledge, whereas telephone access was uncommon, implying that

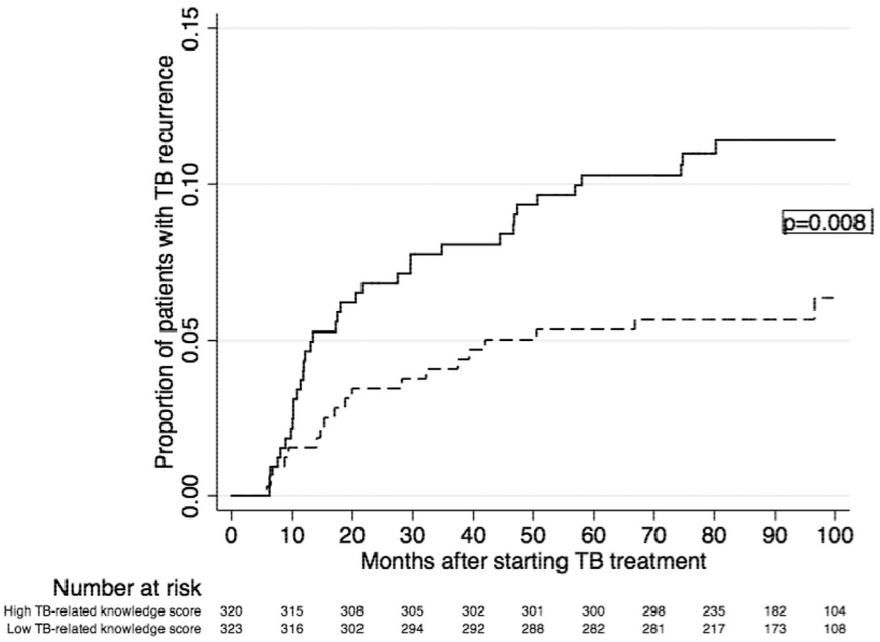

Figure 3 Kaplan–Meier curve demonstrating TB recurrence in patients previously considered cured of TB. The numbers in the table below the graph indicate the number of patients with follow-up data at that time. The hazard ratio (HR) of recurrence was 2.1 times greater ($p = 0.008$) in patients with lower than median TB-related knowledge score (solid line) versus higher than median (dashed line) over a maximum of 10 years follow-up. Analysing only data from shorter durations of follow-up gave similar results: 1 year HR = 2.8, $p = 0.049$; 2 years HR = 2.0, $p = 0.058$; 3 years HR = 2.0, $p = 0.04$; 4 years HR = 1.9, $p = 0.04$; 5 years HR = 2.0, $p = 0.02$; 6 years HR = 1.9, $p = 0.03$; 7 years HR = 2.0, $p = 0.01$; 8 years HR = 2.0, $p = 0.01$ and 9 years HR = 2.0, $p = 0.01$.

using mobile telephones for health promotion may not be well suited to this type of impoverished setting. Patients knew more about TB than people with suspected TB and healthy controls, probably because of patients' recent contact with the healthcare system. Health information should include extra-pulmonary TB symptoms because these symptoms were common but were infrequently recognised as TB-related, as reported elsewhere.[26] Among TB patients, older age and incomplete schooling were independently associated with low TB-related knowledge, as reported previously.[6] High TB-related knowledge was associated with underweight probably because weight loss occurs in more severe TB, which may lead to more exposure to healthcare and hence greater access to associated health information.

The questionnaire characterising TB-related beliefs revealed that malnutrition was thought to be more important for TB control than TB exposure. Whilst this contrasts with mainstream teaching, in this setting most adults already had latent TB infection,[27] so improved nutrition may indeed be as important for reducing personal TB risk as avoiding TB exposure.[28] Awareness of the strong cultural association between TB and nutrition in this setting may be useful for health promotion campaigns.

The median treatment delay of 60 days contrasted with the Peruvian ministry of health target of 14 days of productive cough prior to TB diagnosis and treatment. Low TB-related knowledge was associated with treatment delay in unadjusted analysis and in analysis adjusted for disease severity. However, this was explained by poverty and patient demographics, so in our study TB-related knowledge was not independently associated with treatment delay in analysis adjusted by multiple regression. Nonetheless, previous research in other settings has identified associations between low TB-related knowledge and delayed TB treatment that were independent of confounding factors,[26] which is important because TB patients are most infectious prior to treatment.[29] In our study, older age, female sex and poverty were also associated with delayed treatment, as reported elsewhere.[7,26] Two indicators of TB severity (low body mass index and strongly positive microscopy grade) were also independently associated with longer treatment delay, possibly because delayed treatment allowed TB disease to become more severe.[20]

Adverse early treatment outcome was not associated with TB-related knowledge but was associated with incomplete schooling, as reported elsewhere.[30] We found that 1 in every 11 apparently cured TB patients who were followed-up had again been diagnosed with recurrent TB, mostly soon after apparent cure. This implies that the sputum microscopy-based assessment of cure was insensitive for detecting treatment failure, demonstrating the importance of following-up treated TB patients to confirm persistent cure.[16] Low TB-related knowledge was associated with TB recurrence, including after adjustment for co-morbidities, indicators of disease severity and socio-demographic factors. This is important because TB recurrence increases TB transmission, morbidity and mortality.[31]

We did not differentiate between recurrences caused by TB relapse versus re-infection but both are important

causes of TB recurrence and both have the potential to be prevented by improving TB-related knowledge.[32] For example, TB-related knowledge may decrease the risk of TB recurrence caused by relapse by: reducing treatment intermittency[33]; decreasing gender inequalities[34]; encouraging health-seeking behaviours[23]; and increasing completion of drug-susceptibility testing.[3]; Similarly, TB-related knowledge may decrease the risk of TB recurrence caused by re-infection by: improving nutrition-mediated anti-TB immunity[35]; and by improving ventilation-mediated reduction of airborne TB transmission.[36] Thus, education to increase TB-related knowledge has the potential to reduce these and other risk factors for both TB relapse and re-infection. Whether TB recurrences were principally caused by relapse or reinfection does not affect the importance of our finding that low TB-related knowledge at the time of treatment initiation strongly and independently predicted TB recurrence. Having MDR-TB was also strongly and independently associated with TB recurrence, as reported elsewhere.[37]

Among all participants, male gender was associated with low TB-related knowledge, as in a previous study,[34] consistent with the qualitative finding that in most households in this setting females have greater access to health education.[34] In contrast, in patients there was no sex difference in TB-related knowledge. This may indicate that this healthcare system informed male and female TB patients equally about TB-related issues, as previously reported.[34] In the current study, male gender was also associated with TB recurrence, which appears to be a novel finding compared with previous studies.[38,39]

Limitations to this research include that the healthy control population was recruited only late in the study, not concurrently with the entire recruitment period. However, this is irrelevant to the central findings concerning TB recurrence in patients, because these findings did not involve the healthy control group. Furthermore, a sensitivity analysis indicated that the timing of recruitment did not influence the other study findings. As in all single-site research, the generalizability of these findings should be reassessed in other settings. Our treatment delay assessment was imperfect because it did not differentiate between health-seeking delay and health-system delay, possibly explaining why TB-related knowledge was not independently associated with treatment delay in our study, in contrast to previous research.[26] TB-related knowledge may potentially be associated with both health-seeking delay and also health-system delay by causing patients to present sooner to specific TB services or prompting patients to suggest TB-testing to healthcare professionals. Our recent data in the same region revealed that health-seeking delay constituted the major part of treatment delay.[40] Future research should differentiate health-seeking from health-system delay.

In conclusion, low TB-related knowledge independently predicted a more than doubled-risk of TB recurrence. Most patients had heard about TB from personal networks and this information source was associated with low TB-related knowledge. Our findings add to the evidence that poverty and inadequate education impair TB control.[3] These findings also support including psychosocial interventions such as health education as part of the care provided for people living with TB. Social and economic support have recently been added as core components of World Health Organization policy for TB prevention, care and control and our findings suggest that these interventions should include activities to increase TB-related knowledge because these have the potential to reduce TB recurrence and hence strengthen TB control.[3,41]

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Conflict of interest

All of the authors declare that they have no conflict of interest in relation to this research.

Author contributions

EEW led data analysis, interpretation and manuscript preparation assisted by MAT and EE. RM led data collection. CAE and EL mentored EEW. CAE coordinated the project. All authors edited and approved the manuscript.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jinf.2015.05.010.

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