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The impact of tuberculosis on health utility: a longitudinal cohort study

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Abstract
Purpose To estimate health utility derived from the Short Form-36 (SF-36) questionnaire and Standard Gamble instrument for persons diagnosed and treated for tuberculosis (TB) disease, those diagnosed and treated for latent TB infection (LTBI), and those screened but not treated for TB disease or LTBI over the year following their diagnosis/initial assessment.
Methods Participants were recruited at two Montreal hospitals (2008–2011) and completed the SF-36 and Standard Gamble at baseline and at follow-up visits 1, 2, 4, 6, 9, and 12 months thereafter. SF-6D health utility scores were derived from SF-36 responses. Linear mixed models were used to compare mean health utility at each evaluation and changes in health utility between participants treated for TB disease, those treated for LTBI, and those in the control group.
Results Of the 263 participants, 48 were treated for TB disease, 105 for LTBI, and 110 were control participants. Fifty-four percent were women, mean age was 35 years, and 90 % were foreign-born. Participants treated for TB disease reported worse health utility compared with control participants at the baseline visit (mean SF-6D: 0.69 vs. 0.81; mean Standard Gamble: 0.64 vs. 0.96). They reported successive improvement at months 1 and 2 that was then sustained throughout follow-up. Health utility reported by participants treated for LTBI and control participants was comparable throughout the study.
Conclusion Treatment for TB disease had a substantial negative impact on health utility, particularly during the first 2 months of treatment. However, treatment for LTBI did not have a substantial impact.

Keywords Tuberculosis · Health utility · SF-6D · Standard Gamble · Linear mixed model regression

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Introduction

In a variety of settings, patients treated for tuberculosis (TB) disease report a substantial toll on both physical and psychological aspects of health-related quality of life (HRQOL) [1]. The World Health Organization recommends that patients diagnosed with TB disease be treated with an effective regimen in a setting and manner that is patient-centered, with appropriate support for patients' medical and psychosocial needs [2]. Even for persons with uncomplicated disease, treatment is long and complex,

with the standard drug regimen involving four drugs initially and lasting at least 6 months [3].

Persons diagnosed with latent TB infection (LTBI) in high-income countries receive treatment to prevent subsequent development of TB disease, particularly in the presence of other risk factors such as close contact with a person with TB disease. Patients treated for LTBI most often receive daily isoniazid for 9 months; they may also experience decrements in HRQOL, due to frequent treatment intolerance [4].

In Canada and other high-income countries, a key limitation in decision-making in the areas of TB screening and prevention is the dearth of patient-reported health preferences measured at diagnosis, throughout treatment, and post-treatment. According to a recent systematic review of the literature, few studies have compared health preferences reported by persons treated for TB disease or LTBI with those reported by a comparison group of similar background, who are screened for TB but found not to require treatment [1]. As the majority of persons diagnosed with TB disease or LTBI in Canada are recent immigrants who are economically vulnerable and often not yet employed, a control group of similar background can help to tease apart the impact of TB diagnosis and treatment on health status from other influences such as socioeconomic instability and unemployment in the context of recent immigration [5, 6].

The purpose of this study was to estimate health utility derived from the Short Form-36 (SF-36) and Standard Gamble questionnaires completed by patients diagnosed and treated for TB disease, LTBI, and a screened, untreated group of participants over the year following their diagnosis/initial assessment [7]. These estimates are relevant to understanding the health impact of TB disease, LTBI, and their treatment, and potentially to future cost-utility analyses that may inform health policy and practice.

Methods

Study population and participant recruitment

Participants were recruited between June 2008 and October 2011, at two hospitals in Montreal, Canada—the Montreal Chest Institute (MCI) and the Sir Mortimer B. Davis—Jewish General Hospital (JGH). The MCI and the JGH are two of three adult health care centers that operate specialized TB clinics in the Montreal area. From 1996 to 2007, 29 and 14 % of patients treated for active TB in Montreal were treated at the MCI and JGH, respectively [8]. Participants were referred to these two centers for a variety of reasons including the following: suspected TB disease based on symptoms and/or chest radiography; LTBI based on tuberculin skin test (TST) results plus clinical and radiographic evaluation; screening for TB in several contexts including known contact with TB disease, newly arrived immigrants and refugee claimants, and health care training or work. Reason for referral was captured at the initial evaluation of potential participants.

Participants with TB had culture-confirmed disease; some (those with initially more severe disease and/or who posed a greater contagion risk) were initially hospitalized and subsequently treated as outpatients, while others were treated solely as outpatients. Those treated for LTBI were diagnosed with asymptomatic infection, typically based on positive TST results, sometimes with positive Interferon-γ Release Assay (IGRA) results and/or chest radiographic scarring. They were recruited to the study within 2 weeks of treatment initiation. Participants in the control group were evaluated for possible TB and had negative test results. These participants were found not to require treatment of any kind.

Exclusion criteria included the following: (1) multi-drug resistant (MDR) TB disease, (2) acute altered mental state or chronic confusion, (3) major psychiatric disorder (e.g., bipolar disorder, schizophrenia) having required hospitalization or a change in psychiatric medication in the last year, or (4) presence of another diagnosed acute or chronic health condition, requiring treatment and/or likely to impact the participant's HRQOL (e.g., diabetes, hypertension, coronary artery disease, malignancy, HIV infection requiring antiretroviral therapy). Additionally, we excluded individuals who were unable to understand and communicate in English or French, or who were younger than 18 years of age.

Frequency matching by immigrant status was used to ensure a balance of the proportion of immigrants across the three participant groups. For every ten participants recruited to the group treated for TB disease, the proportions of immigrants among participants treated for LTBI and among the control group were compared with that of the group treated for TB disease, with recruitment of the subsequent LTBI and control group participants adjusted accordingly.

Study procedure

At the baseline interview, participants were evaluated for language ability and completed questionnaires describing their socio-demographic (including immigration status) and clinical characteristics. They completed HRQOL and health utility evaluations, see below. This initial interview took place within 2 weeks after treatment initiation among those participants treated for TB disease or LTBI, or 2 weeks from the medical assessment for participants in the control group. The interviewer then reviewed participants' medical

charts to verify their responses and extract additional relevant clinical information.

Participants were again interviewed at 1, 2, 4, 6, 9, and 12 months post-baseline; these time points correspond to important milestones in TB treatment regimens [3]. HRQOL and health utility were captured at these follow-up visits as were patient-reported adverse events and changes to treatment regimens since the previous visit. Prospective clinical information gathered from participants was verified in their medical charts at each interview. We conducted double data entry and resolved discrepancies against paper source documents and by consensus discussion where appropriate.

Participants' written informed consent was obtained before the initial interview. Research ethics committee approval was obtained from both the MCI and JGH. The study was performed in accordance with the ethical standards established in the 1964 declaration of Helsinki and its later amendments. To compensate participants for the time needed to complete study measurements, an international telephone calling card worth $10 CAD was provided at the end of each visit. Participants were compensated for any travel expenses incurred to complete each visit.

HRQOL and health utility measures

Two sets of health utility scores were calculated in this study—the indirectly estimated SF-6D health utility scores from the SF-36 questionnaire and the directly estimated health utility scores from the Standard Gamble questionnaire. The SF-36 is a widely used instrument that assesses self-reported HRQOL [7]. Health utility scores are indirectly estimated from SF-36 item responses by constructing the SF-6D metric, which is composed of 11 items, representing six domains. Transformation of relevant SF-36 responses to SF-6D utility scores was described by Brazier et al. [9, 10], who provided a multi-attribute utility function derived from the general population of the United Kingdom. The SF-6D reports health utility on a scale ranging from 0 (death) to 1 (perfect health). We validated the SF-36 written questionnaire in English and French for Canada in our pilot study [11].

With the Standard Gamble, participants were asked to choose between the certainty of their current health state for the subsequent 10 years concluding in immediate and painless death or a hypothetical gamble. This gamble involved x probability of perfect health for 10 years followed by immediate and painless death and $1-x$ probability of immediate and painless death [12]. The final health utility was reported on a scale from 0 (death) to 1 (perfect health as imagined by the respondent). The script validated in our earlier pilot study was used in every administration of the Standard Gamble questionnaire [13]. This script includes an assessment of hypothetical "marker" health states with mild, moderate, and severe health disturbance. Participants were then asked about their own health state. This order was followed uniformly for all evaluations. The script and marker health states are provided in Online Resource 1. Additionally, a probability wheel (an adjustable pie chart containing two colors) was used to help participants understand the choice between 100 % certainty of the health state being evaluated and the varying probabilities of the gamble.

Statistical analyses

The three participant groups were described according to baseline socio-demographic characteristics, and clinical features captured at the initial and follow-up visits. The distribution of health utility scores was summarized for each participant group at each evaluation. The main association of interest was between participant group and health utility over the year following the initial assessment, estimated with either the SF-6D or the Standard Gamble. Characteristics considered a priori confounders of this association were examined quantitatively using either (1) Pearson's χ^2 test or Fisher's exact test or (2) Student's T test to test for associations between participant group and categorical variables or continuous variables, respectively [14–16]. Simple linear mixed models were used to evaluate the association between potential confounders and mean health utility scores [17]. An a priori level of statistical significance was set at p value $= 0.05$. Crude effect sizes, examining change in health utility over time within each participant group, were calculated and evaluated using Cohen's criteria [18]. A minimal clinically important difference is not known in the TB context, so it was considered a priori that effect sizes ≥ 0.50 indicated a statistically meaningful change in health utility scores.

For each of the two health utility measures, multivariable linear mixed models were used to compare scores over the 12-month study period, between (1) participants treated for TB disease versus the control group, and (2) participants treated for LTBI versus the control group [19]. The control group was the referent group for all models. A time × participant group interaction term was included to account for different health utility score patterns over time between the participant groups. Random intercepts, random slopes, and spatial covariance structures using visit number were also incorporated into the models. Age at baseline, sex, and additional factors determined to be important confounders of the association between participant group and health utility were included as covariates in all adjusted models. Model fit was assessed using the Akaike information criterion (AIC) [19]. Mean-adjusted

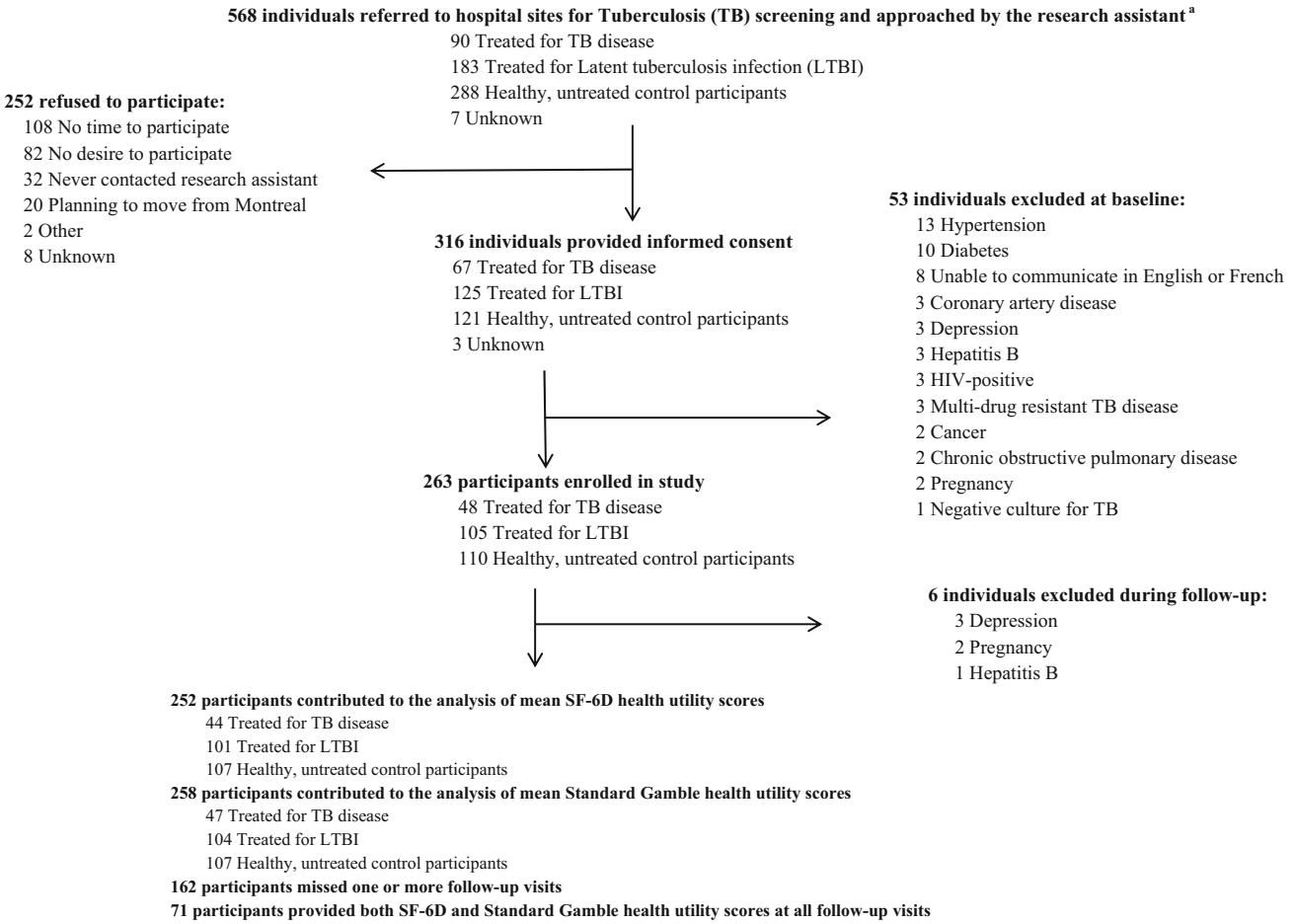

Fig. 1 Participant selection in longitudinal study with recruitment from June 2008 to October 2011

health utility scores for each participant group at each evaluation period were calculated from final model estimates. Changes in adjusted health utility between successive interviews and from baseline were also calculated from these estimates. Parametric 95 % confidence intervals (CI) were calculated for adjusted estimates of mean and change in mean health utility scores [19]. Sample size calculations indicated that 40 participants treated for TB disease should be recruited to the study to detect a change in health utilities of 0.003/month over 12 months with 80 % power, $\rho = 0.8$, and p value $= 0.05$. More details on sample size calculations are provided in Online Resource 1. Methods used in sensitivity analyses of the potential impact of (1) ceiling effects of health utility scores evaluated with the Standard Gamble, (2) missing data, and (3) selection bias due to missed visits or participants lost to follow-up are also presented in Online Resource 1. All statistical analyses were conducted using SAS statistical software (version 9.3; SAS Institute, Cary NC); graphs were created using Microsoft Excel (2010; Redmond, WA, United States) [20, 21].

Results

Study sample

A total of 568 individuals were referred to either the MCI or the JGH TB services and approached by the research assistant, of whom 316 (56 %) provided informed consent for study participation (Fig. 1). Individuals who agreed to participate and who refused were similar in mean age—35 years for the former group and 36 years for the latter. However, 60 % of the group who refused to participate were men, and the refusal rate was higher among the group screened for TB but found not to require treatment (67 %) compared with those diagnosed with TB disease (9 %) and those diagnosed with LTBI (23 %) (Table 1 in Online Resource 2). The most common reasons for refusing participation were no time to participate (108 individuals, 43 %) and no desire to participate (82 individuals, 33 %) (Fig. 1). Of the 316 individuals who provided informed consent, 53 (17 %) were found to be ineligible at baseline. Individuals excluded were on average older than study

Table 1 Participant characteristics at the initial interview by participant group and sex ($N = 263$)

Characteristics	Total			Treated for tuberculosis disease			Treated for latent tuberculosis infection			Screened for tuberculosis but healthy and untreated		
	Total (%)	Men (%)	Women (%)	Total (%)	Men (%)	Women (%)	Total (%)	Men (%)	Women (%)	Total (%)	Men (%)	Women (%)
Sample size	263	122 (46)	141 (54)	48 (18)	27 (56)	21 (44)	105 (40)	45 (43)	60 (57)	110 (42)	50 (45)	60 (55)
Mean (standard deviation) age, years	35 (9)	35 (10)	34 (9)	37 (12)	38 (15)	36 (7)	33 (9)	34 (9)	33 (10)	35 (8)	34 (8)	35 (8)
Region of origin												
Africa	78 (30)	46 (38)	32 (23)	15 (31)	12 (44)	3 (13)	29 (28)	18 (40)	11 (19)	34 (31)	16 (32)	18 (30)
Asia	67 (25)	27 (22)	40 (28)	18 (38)	8 (29)	10 (47)	28 (27)	8 (18)	20 (33)	21 (19)	11 (22)	10 (17)
Eastern Europe	20 (8)	9 (7)	11 (8)	3 (6)	1 (4)	2 (10)	5 (5)	3 (7)	2 (3)	12 (11)	5 (10)	7 (12)
Western Europe	16 (6)	9 (7)	7 (5)	1 (2)	1 (4)	0 (0)	5 (5)	3 (7)	2 (3)	10 (9)	5 (10)	5 (8)
Central America	41 (16)	14 (12)	27 (19)	3 (6)	1 (4)	2 (10)	20 (18)	6 (13)	14 (24)	18 (16)	7 (14)	11 (18)
North America	27 (10)	12 (10)	15 (11)	5 (11)	3 (11)	2 (10)	11 (10)	5 (11)	6 (10)	11 (10)	4 (8)	7 (12)
South America	14 (5)	5 (4)	9 (6)	3 (6)	1 (4)	2 (10)	7 (7)	2 (4)	5 (8)	4 (4)	2 (4)	2 (3)
Median (Inter-Quartile Range) duration in Canada (years)	3 (1, 9)	2 (1, 7)	3 (1, 10)	2 (0, 7)	2 (0, 10)	2 (0, 7)	3 (1, 9)	1 (0, 6)	5 (2, 10)	2 (1, 9)	2 (1, 7)	2 (1, 9)
Reason for hospital referral												
Pre-landing refugee or immigrant screening	32 (12)	18 (15)	14 (10)	9 (19)	5 (19)	4 (19)	6 (6)	3 (7)	3 (5)	17 (15)	10 (20)	7 (12)
Post-landing surveillance	25 (10)	14 (11)	11 (8)	7 (15)	3 (11)	4 (19)	11 (10)	7 (16)	4 (7)	7 (6)	4 (8)	3 (5)
Tuberculin skin test, not contact of TB patient	132 (50)	49 (40)	83 (59)	1 (2)	0 (0)	1 (5)	64 (61)	22 (49)	42 (70)	67 (61)	27 (54)	40 (67)
Contact of tuberculosis patient	24 (9)	13 (11)	11 (8)	1 (2)	0 (0)	1 (5)	18 (17)	10 (22)	8 (13)	5 (5)	3 (6)	2 (3)
Symptomatic of tuberculosis disease[a]	24 (9)	17 (14)	7 (5)	24 (50)	17 (63)	7 (33)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Other	12 (5)	5 (4)	7 (5)	6 (13)	2 (7)	4 (19)	6 (6)	3 (7)	3 (5)	0 (0)	0 (0)	0 (0)
Unknown	14 (5)	6 (5)	8 (6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	14 (13)	6 (12)	8 (13)
Smoking status												
Ever cigarette smoker[b]	65 (25)	43 (35)	22 (16)	18 (38)	14 (52)	4 (19)	24 (23)	15 (33)	9 (15)	23 (21)	14 (28)	9 (15)
Current cigarette smoker[c]	29 (11)	19 (16)	10 (7)	11 (23)	9 (33)	2 (10)	8 (8)	5 (11)	3 (5)	10 (9)	5 (10)	5 (8)
Median (IQR) pack-years smoking	8 (3, 18)	8 (1, 18)	5 (3, 14)	13 (6, 19)	17 (8, 20)	5 (3, 9)	4 (1, 16)	2 (1, 16)	5 (2, 12)	6 (3, 18)	5 (1, 18)	6 (4, 21)

[a] Common symptoms of TB disease include chronic cough of at least 2 weeks' duration, fever, and night sweats. Other symptoms may include hemoptysis, anorexia, weight loss, and chest pain

[b] A participant who never smoked is someone who smoked less than 20 packs of cigarettes or 400 g of tobacco in a lifetime or <1 cigarette a day for 1 year

[c] A participant who is a current smoker smoked cigarettes as of 1 month before the initial interview

participants (Table 1 in Online Resource 2). The most frequent reasons for exclusion were concomitant hypertension or diabetes (Table 2 in Online Resource 2).

Of the 263 eligible participants, 48 were diagnosed and treated for TB disease, 105 were diagnosed and treated for LTBI, and 110 were control participants. During follow-up, an additional three participants were diagnosed with depression, two became pregnant, and one was diagnosed with hepatitis B and were therefore excluded from participating in subsequent study assessments (Fig. 1). By the 12-month visit, 71 participants provided *both* SF-6D and Standard Gamble health utility data at *all* follow-up visits—18 (25 %) participants treated for TB disease, 20 (28 %) participants treated for LTBI, and 33 (47 %) participants in the control group. One hundred and sixty-two participants missed at least one follow-up visit—21 (13 %) treated for TB disease, 76 (47 %) treated for LTBI, and 65 (40 %) in the control group. Proportions of men and women and mean age were comparable between participants who attended visits and those who missed visits (Table 3 in Online Resource 2). The proportion of participants retained for interviews was highest among those treated for TB disease, with 85 % retained through the 6-month visit—the duration of standard, compulsory treatment, and attendant close follow-up.

Participant characteristics

Key characteristics reported by participants at the first interview are described in Table 1; clinical characteristics reported in participants' medical charts at the baseline assessment are shown in Table 4 of Online Resource 2. Fifty percent of the total sample was referred to a study site for a TST result, but were not contacts of persons with TB. This group represented over 60 % of the participants treated for LTBI and the control group. Fifty percent of the participants treated for TB disease were referred to a study site because of symptoms (Table 1). Ninety percent of the participants were foreign-born; most originated from countries of Africa (78, 30 %) or countries of Asia (67, 25 %), but more than half were Canadian citizens or permanent residents (Table 1). Thirty-two percent of all participants reported missing some work or school due to their diagnosis and/or treatment during the study period. This proportion was much greater among the group treated for TB disease (63 %), who reported missing a median of 14.0 days of work or school (interquartile range (IQR): 7.0, 21.0).

Forty (83 %) participants treated for TB disease had pulmonary disease. Of these, 13 (33 %) had cavitary disease. Twenty (42 %) of the participants treated for TB disease received directly observed therapy. Twenty-two (46 %) participants treated for TB disease were hospitalized with a median (IQR) duration of hospital stay of 14 days (11, 23) (Table 4 in Online Resource 2). Of the participants treated for LTBI, 20 (19 %) had abnormal chest radiographs. All participants treated for LTBI self-administered their medication (Table 4 in Online Resource 2). At the initial assessment, a greater proportion of participants treated for TB disease reported at least one other (concomitant) health condition or one other medication (67 and 60 %, respectively) compared with participants treated for LTBI (30 and 10 %, respectively) or control participants (12 and 5 %, respectively) (Table 4 in Online Resource 2).

Sixteen (34 %) participants treated for TB disease and 20 (38 %) participants treated for LTBI reported at least one episode of treatment intolerance between the baseline and 1-month evaluations; gastrointestinal complaints were the most common. These numbers decreased from 1-month through the 9-month visits. Among participants treated for TB disease, there were ten reports of at least one medication stopped earlier than expected due to adverse events. Among participants treated for LTBI, there were seven reports of stopping isoniazid before the expected 9 months of treatment and one report of stopping rifampin before the expected 4 months of treatment, due to adverse events. No participant experienced an adverse event that led to hospitalization.

Findings from univariable analyses

At the baseline evaluation, mean SF-6D health utility scores reported by participants treated for TB disease were significantly worse than those reported by the other two participant groups (Table 2; Fig. 2). From the baseline to the 1-month evaluation, there was a clinically meaningful improvement in mean SF-6D health utility scores among participants treated for TB disease (effect size = 0.5), primarily among women (effect size = 0.7) [18] (Table 2). From the 2- through 6-month visits, mean SF-6D health utility scores were comparable across the three participant groups. At the 9- and 12-month visits, however, participants treated for TB disease reported the highest mean scores of the three participant groups. Compared with health utility scores reported at baseline, clinically meaningful improvements in mean scores were observed at the 2-, 4-, 6-, 9-, and 12-month visits among both men and women treated for TB disease (Table 2).

Participants treated for TB disease reported the lowest and the control group reported the highest mean Standard Gamble health utility scores throughout the study period (Table 3; Fig. 3). From the baseline to the 1-, 2-, and 4-month visits, we observed clinically meaningful improvements in mean Standard Gamble health utility scores reported by participants treated for TB disease, primarily among women. From the baseline to the 6-, 9-,

Table 2 Mean SF-6D health utility scores and effect sizes at each visit by participant group and sex ($N = 252$)

Visit	Categories of participants by sex	Treated for tuberculosis disease					Treated for latent tuberculosis infection					Screened for tuberculosis but healthy and untreated				
		N	%	Mean utility (standard deviation)	Effect size[a] $_1$	Effect size[b] $_2$	*N*	%	Mean utility (standard deviation)	Effect size$_1$	Effect size$_2$	*N*	%	Mean utility (standard deviation)	Effect size$_1$	Effect size$_2$
Baseline	Total	44	–	0.69 (0.14)	–	–	101	–	0.81 (0.11)	–	–	107	–	0.81 (0.12)	–	–
	Men	24	55	0.69 (0.15)	–	–	43	43	0.84 (0.09)	–	–	48	45	0.84 (0.11)	–	–
	Women	20	45	0.69 (0.12)	–	–	58	57	0.79 (0.12)	–	–	59	55	0.79 (0.13)	–	–
1 Month	Total	43	–	0.76 (0.15)	**0.5**	–	77	–	0.79 (0.12)	−0.2	–	91	–	0.82 (0.12)	0.1	–
	Men	23	53	0.75 (0.14)	0.4	–	30	39	0.83 (0.12)	−0.1	–	44	48	0.84 (0.13)	0.0	–
	Women	20	47	0.78 (0.15)	**0.7**	–	47	61	0.77 (0.11)	−0.2	–	47	52	0.80 (0.12)	0.1	–
2 Months	Total	43	–	0.82 (0.14)	**0.9**	0.4	68	–	0.80 (0.11)	−0.1	0.1	87	–	0.82 (0.12)	0.1	0.0
	Men	25	58	0.81 (0.13)	**0.9**	0.4	30	44	0.83 (0.10)	−0.1	0.0	40	46	0.86 (0.11)	0.2	0.2
	Women	18	42	0.82 (0.15)	**1.0**	0.3	38	56	0.77 (0.11)	−0.2	0.0	47	54	0.79 (0.12)	0.0	−0.1
4 Months	Total	38	–	0.80 (0.14)	**0.8**	−0.1	68	–	0.80 (0.13)	−0.1	0.0	70	–	0.82 (0.11)	0.1	0.0
	Men	21	55	0.80 (0.14)	**0.8**	−0.1	30	44	0.84 (0.12)	0.0	0.1	29	41	0.83 (0.11)	−0.1	−0.3
	Women	17	45	0.79 (0.15)	**0.7**	−0.2	38	56	0.76 (0.13)	−0.2	−0.1	41	59	0.81 (0.11)	0.2	0.2
6 Months	Total	40	–	0.81 (0.14)	**0.9**	0.1	54	–	0.80 (0.12)	−0.1	0.0	61	–	0.83 (0.13)	0.2	0.1
	Men	23	58	0.80 (0.14)	**0.8**	0.0	26	48	0.84 (0.10)	0.0	0.0	29	48	0.83 (0.12)	−0.1	0.0
	Women	17	42	0.81 (0.15)	**0.9**	0.1	28	52	0.76 (0.14)	−0.2	0.0	32	52	0.82 (0.13)	0.2	0.1
9 Months	Total	33	–	0.85 (0.11)	**1.3**	0.3	54	–	0.79 (0.13)	−0.2	−0.1	55	–	0.81 (0.13)	0.0	−0.2
	Men	19	58	0.85 (0.12)	**1.2**	0.4	28	52	0.81 (0.12)	−0.3	−0.3	21	38	0.84 (0.12)	0.0	0.1
	Women	14	42	0.86 (0.10)	**1.5**	0.4	26	48	0.77 (0.13)	−0.2	0.1	34	62	0.80 (0.14)	0.1	−0.1
12 Months	Total	29	–	0.86 (0.11)	**1.4**	0.1	49	–	0.82 (0.12)	0.1	0.2	59	–	0.84 (0.12)	0.2	0.2
	Men	17	59	0.85 (0.10)	**1.3**	0.0	25	51	0.82 (0.12)	−0.2	0.1	27	46	0.86 (0.10)	0.2	0.2
	Women	12	41	0.86 (0.13)	**1.4**	0.0	24	49	0.82 (0.12)	0.2	0.4	32	54	0.82 (0.14)	0.2	0.1

Effect size conveys the estimated magnitude in differences in two measures of health utility scores. An effect size >0.50 indicates a statistically meaningful change in mean SF-6D health utility scores and is indicated in bold font. [18]

[a] Effect Size$_1$ is the effect size of the change in mean SF-6D health utility scores from the baseline visit to the given visit

[b] Effect size$_2$ is the effect size of the change in mean SF-6D health utility scores from the previous visit to the given visit, e.g., effect size$_2$ for the 4-month visit is the effect size of the changes in mean SF-6D health utility scores from the 2-month visit to the 4-month visit

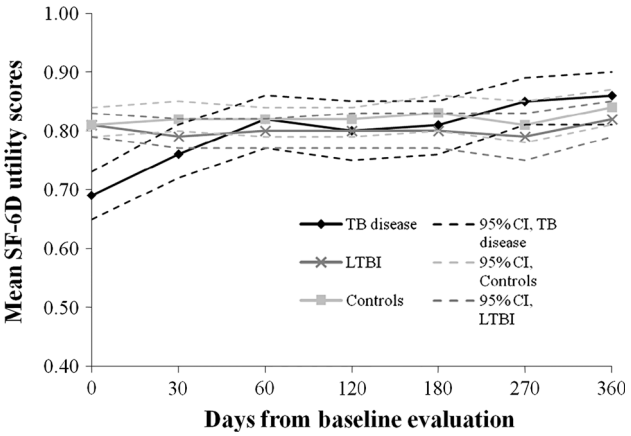

Fig. 2 Mean SF-6D utility scores and 95 % confidence intervals reported at each visit by participant group

and 12-month visits, improvements in Standard Gamble health utility scores were observed among both men and women treated for TB disease.

Findings from multivariable analyses

Even after adjustment, mean health utility scores reported by participants treated for TB disease were significantly different from control participants at baseline—participants treated for TB disease and control participants reported mean-adjusted SF-6D health utility scores (95 % CI) of 0.72 (0.65, 0.79) and 0.86 (0.79, 0.93), respectively, and mean Standard Gamble health utility scores of 0.75 (0.66, 0.83) and 1.00 (0.95, 1.00), respectively (Tables 4, 5). Mean health utility scores reported by participants treated for TB disease significantly improved during the first month of treatment—mean SF-6D health utility scores improved by 0.08 (95 % CI: +0.04, +0.12; p value = 0.01) and mean Standard Gamble health utility scores improved by 0.15 (95 % CI: +0.10, +0.21; p value < 0.0001) (Tables 1–4 in Online Resource 3). Mean SF-6D health utility scores also improved significantly (+0.06, 95 % CI: +0.01, +0.11; p value = 0.03) from the 6- to the 9-month evaluations (Table 2 in Online Resource 3). Mean Standard Gamble health utility scores were somewhat lower among participants treated for LTBI than among control participants; however, there was only a statistically significant difference between the mean Standard Gamble health utility scores reported by these two groups at the baseline evaluation (Table 5).

Findings from mean Standard Gamble health utility scores using longitudinal tobit regression were similar to results of analyses using linear mixed model regression. Results of linear mixed model regression including multiple imputation of missing data yielded similar results to those of the main models. Differences in mean healthy utility scores of participants who attended visits, missed visits, and lost to follow-up were likely due to random variation. (results from sensitivity analyses not shown.)

Discussion

In this longitudinal study among a diverse immigrant population seen for TB treatment and/or screening in Montreal, TB disease had a significant impact on health utility during the initial treatment phase. Participants treated for TB disease reported substantially improved health utility by 2 months of treatment, which was sustained. On the other hand, treatment for LTBI was not associated with any notable decrements in health utility since utility scores did not differ substantially between persons treated for LTBI and the control group. Similarly, utility scores did not change during follow-up among participants treated for LTBI.

Sample characteristics highlight some key considerations for treating patients with TB in settings similar to ours. The overwhelming majority of participants were foreign-born. In addition to the typical stressors faced by the immigrant population, approximately one-third of the participants reported missing some work or school due to their diagnosis and/or treatment; this was even more pronounced among participants treated for TB disease. Furthermore, almost half of the participants treated for TB disease were hospitalized for their illness. To provide patient-centered treatment for TB addressing both medical and psychosocial needs, health professionals and policy makers should consider these challenges.

Our findings are similar to other published studies. Guo et al. [22] reported worse health utility among participants treated for TB disease compared with participants treated for LTBI, within 2 months of treatment initiation, using the SF-6D, Health Utility Index (HUI) 2, and HUI 3 health utility scores. Dion et al. [11, 13] reported similar findings within the first 2 weeks of treatment using the EuroQoL-5D (EQ-5D) and Standard Gamble questionnaires. Kruijshaar et al. [23] reported improvement in health utility (using the EQ-5D) throughout the first 2 months of treatment for TB disease that was similar to our findings. Health utility scores reported at the initial evaluation by our participants treated for TB disease were comparable with recently published health utility scores of individuals in a US-based registry diagnosed with non-small cell lung carcinoma, or with chronic obstructive pulmonary disease or asthma [24].

Our study is the first to evaluate health utility of individuals treated for TB disease, LTBI, and a concurrent comparison group at each milestone of TB treatment. With a similar demographic profile to those treated for TB, this

Table 3 Mean Standard Gamble health utility scores and effect sizes at each visit by participant group and sex ($N = 258$)

Visit	Categories of participants by sex	Treated for tuberculosis disease					Treated for latent tuberculosis infection					Screened for tuberculosis but healthy and untreated				
		N	%	Mean utility (standard deviation)	Effect size$_1$[a]	Effect size$_2$[b]	*N*	%	Mean utility (standard deviation)	Effect size$_1$	Effect size$_2$	*N*	%	Mean utility (standard deviation)	Effect size$_1$	Effect size$_2$
Baseline	Total	47	–	0.64 (0.34)	–	–	104	–	0.89 (0.21)	–	–	107	–	0.96 (0.09)	–	–
	Men	26	55	0.65 (0.37)	–	–	45	43	0.93 (0.15)	–	–	50	47	0.95 (0.12)	–	–
	Women	21	45	0.63 (0.32)	–	–	59	57	0.87 (0.25)	–	–	57	53	0.97 (0.06)	–	–
1 Month	Total	43	–	0.80 (0.22)	**0.6**	–	78	–	0.86 (0.25)	−0.1	–	88	–	0.94 (0.11)	−0.2	–
	Men	22	51	0.76 (0.26)	0.3	–	31	40	0.91 (0.19)	−0.1	–	43	49	0.92 (0.14)	−0.2	–
	Women	21	49	0.83 (0.17)	**0.8**	–	47	60	0.82 (0.27)	−0.2	–	45	51	0.96 (0.08)	−0.1	–
2 Months	Total	44	–	0.80 (0.24)	**0.5**	0.0	68	–	0.87 (0.22)	−0.1	0.0	84	–	0.91 (0.19)	−0.3	−0.1
	Men	25	57	0.74 (0.29)	0.3	−0.1	30	44	0.86 (0.26)	−0.3	−0.2	40	48	0.92 (0.14)	−0.2	0.0
	Women	19	43	0.88 (0.12)	**1.0**	0.3	38	56	0.88 (0.17)	0.0	0.3	44	52	0.91 (0.22)	−0.4	−0.3
4 Months	Total	38	–	0.80 (0.25)	**0.5**	0.0	67	–	0.86 (0.22)	−0.1	0.0	70	–	0.94 (0.12)	−0.3	0.1
	Men	20	53	0.79 (0.26)	0.4	0.2	29	43	0.91 (0.16)	−0.1	0.2	29	41	0.90 (0.17)	−0.3	−0.1
	Women	18	47	0.82 (0.25)	**0.7**	−0.3	38	57	0.83 (0.25)	−0.2	−0.2	41	59	0.95 (0.08)	−0.3	0.2
6 Months	Total	37	–	0.83 (0.23)	**0.7**	0.1	55	–	0.90 (0.17)	0.1	0.2	59	–	0.95 (0.11)	−0.1	0.2
	Men	19	51	0.82 (0.23)	**0.6**	0.1	27	49	0.94 (0.10)	0.1	0.2	28	47	0.95 (0.14)	0.0	0.3
	Women	18	49	0.83 (0.24)	**0.7**	0.0	28	51	0.86 (0.21)	0.0	0.1	31	53	0.96 (0.07)	−0.2	0.1
9 Months	Total	32	–	0.86 (0.22)	**0.8**	0.1	54	–	0.90 (0.16)	0.1	0.0	56	–	0.93 (0.16)	−0.2	−0.1
	Men	17	53	0.85 (0.24)	**0.6**	0.1	28	52	0.93 (0.12)	0.0	−0.1	22	39	0.92 (0.21)	−0.2	−0.2
	Women	15	47	0.88 (0.19)	**1.0**	0.2	26	48	0.86 (0.18)	0.0	0.0	34	61	0.94 (0.11)	−0.3	−0.2
12 Months	Total	28	–	0.89 (0.21)	**0.9**	0.1	50	–	0.91 (0.16)	0.1	0.1	58	–	0.97 (0.06)	0.1	0.3
	Men	15	54	0.86 (0.25)	**0.7**	0.0	26	52	0.92 (0.15)	−0.1	−0.1	26	45	0.96 (0.07)	0.1	0.3
	Women	13	46	0.92 (0.15)	**1.2**	0.2	24	48	0.90 (0.17)	0.1	0.2	32	55	0.98 (0.04)	0.2	**0.5**

Effect size conveys the estimated magnitude in differences in two measures of health utility scores. An effect size >0.50 indicates a statistically meaningful change in mean Standard Gamble health utility scores and is indicated in bold font. [18]

[a] Effect Size$_1$ is the effect size of the change in mean Standard Gamble health utility scores from the baseline visit to the given visit

[b] Effect size$_2$ is the effect size of the change in mean Standard Gamble health utility scores from the previous visit to the given visit, e.g., effect size$_2$ for the 4-month visit is the effect size of the changes in mean Standard Gamble health utility scores from the 2-month visit to the 4-month visit

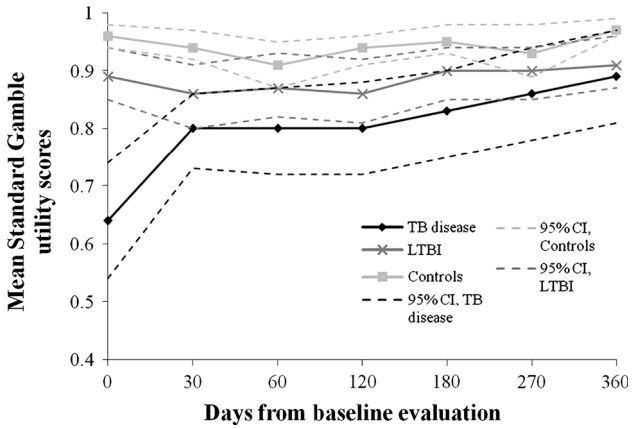

Fig. 3 Mean Standard Gamble utility scores and 95 % confidence intervals reported at each visit by participant group

control group can account for changes in health status apart from TB, in a predominantly immigrant population. The health utility scores reported in this study may be used in cost-utility analyses of TB control programs in high-resource settings similar to ours. Furthermore, our findings emphasize the need for such analyses to take into account differences in health utility across TB treatment groups.

Health utility scores based on the two different instruments were generally similar, with respect to our major findings. Each instrument has advantages and disadvantages. Although the Standard Gamble is considered a "gold standard" for health utility assessment, because it incorporates uncertainty, it can be time-consuming, and it requires respondents to work with probabilities, which are not always easily understood. This is of particular concern to newly arrived immigrants, especially women, who may lack health literacy [25]. Furthermore, the Standard Gamble had important ceiling effects. To streamline research and encourage comparisons across studies and patient groups, the SF-6D may therefore be preferable.

There are a number of limitations to our study. First, we were unable to document health utility before diagnosis, which tends to underestimate the overall impact of TB disease. A previous survey of symptomatic patients with TB disease at the MCI suggested that these patients experience a mean of 3 months of symptoms before diagnosis [26]. Hence, it may be appropriate to "back-extrapolate" initial utility scores according to symptom duration, in order to better gauge the true disutility that results from TB disease.

Second, the SF-6D reflects a scoring function derived from the general population of the United Kingdom, which is different from our study population, and indeed, from groups to whom our results might be extrapolated [10]. The fact that we observed similar patterns in scores with both

Table 4 Mean SF-6D health utility scores reported at each follow-up visit by participant group

Visit	Crude estimate	Adjusted estimate[a]	95 % confidence interval Adjusted estimate	*p* value*
Baseline				
Tuberculosis disease	0.69	0.72	0.65, 0.79	<0.0001*
Latent tuberculosis infection	0.81	0.84	0.79, 0.89	0.70
Control[b]	0.81	0.86	0.79, 0.93	–
1 Month of treatment				
Tuberculosis disease	0.77	0.80	0.73, 0.87	0.29
Latent tuberculosis infection	0.79	0.82	0.76, 0.87	0.25
Control	0.82	0.88	0.81, 0.95	–
2 Months of treatment				
Tuberculosis disease	0.81	0.85	0.77, 0.92	0.16
Latent tuberculosis infection	0.79	0.82	0.77, 0.88	0.17
Control	0.81	0.86	0.80, 0.91	–
4 Months of treatment				
Tuberculosis disease	0.81	0.85	0.77, 0.92	0.27
Latent tuberculosis infection	0.79	0.83	0.76, 0.89	0.24
Control	0.82	0.88	0.81, 0.95	–
6 Months of treatment				
Tuberculosis disease	0.81	0.85	0.77, 0.92	0.92
Latent tuberculosis infection	0.80	0.82	0.77, 0.88	0.99
Control	0.82	0.87	0.80, 0.95	–
9 Months of treatment				
Tuberculosis disease	0.86	0.91	0.83, 0.98	0.70
Latent tuberculosis infection	0.78	0.82	0.76, 0.88	0.56
Control	0.81	0.87	0.80, 0.95	–
12 Months of treatment				
Tuberculosis disease	0.86	0.91	0.83, 0.98	0.39
Latent tuberculosis infection	0.81	0.84	0.78, 0.90	0.37

Table 4 continued

Visit	Crude estimate	Adjusted estimate[a]	95 % confidence interval Adjusted estimate	*p* value*
Control	0.83	0.89	0.81, 0.96	–

* Indicates a *p* value less than 0.05 meaning a statistically significant difference in mean SF-6D health utility scores reported by the group of treated participants and the participants in the untreated control group in the adjusted model, at the given visit

[a] Adjusted models comparing participants treated for TB disease with those participants in the untreated control group controlled for age at baseline, sex, student status at baseline (student/not a student), and other health problems (yes/no) reported by participants at baseline. Adjusted models comparing participants treated for LTBI with those participants in the untreated control group controlled for age at baseline, sex, other health problems (yes/no), and number of days of work or school missed due to diagnosis and treatment of condition

[b] Control is a participant screened for TB who tested negative for TB and was found not to require treatment

the SF-6D and the Standard Gamble tends to allay this concern somewhat.

Third, selection bias is an important concern. Participation in this study required substantial French or English language skills and literacy. Immigrants in Canada who cannot communicate in either official language are more vulnerable with respect to TB and likely to report worse health utility. However, in our sample, language skills only resulted in eight individuals being ineligible for participation—as those whose limited French and English were evident were not approached for participation (Table 2 in Online Resource 2].

Fourth, we had little data about persons who were approached but refused to participate; similarly, in most cases, we could not assess reasons for study dropout. Dropouts are of particular concern with respect to participants treated for LTBI, since it is possible that participants who experienced particularly disruptive adverse events were most likely to stop their medication on their own, and also to drop out. However, differences in preceding mean utility scores among participants who attended, missed, and lost to follow-up at the following visit were very limited.

Fifth, a ceiling effect was evident for Standard Gamble health utility scores, which may violate an assumption of linear mixed model regression. However, findings from sensitivity analyses using longitudinal tobit regression, taking into account such ceiling effects, confirmed the main results.

Finally, we conducted our study in a low TB incidence setting with considerable resources. Our health utility estimates may not necessarily be generalizable to high-incidence, resource-limited settings. Similarly, some

Table 5 Mean Standard Gamble health utility scores reported at each follow-up visit by participant group

Visit	Crude estimate	Adjusted estimate[a]	95 % confidence interval Adjusted estimate	*p* value*
Baseline				
Tuberculosis disease	0.64	0.75	0.66, 0.83	<0.0001*
Latent tuberculosis infection	0.89	1.00	0.93, 1.00	0.005*
Control[b]	0.96	1.00	0.95, 1.00	–
1 Month of treatment				
Tuberculosis disease	0.79	0.90	0.81, 0.99	0.31
Latent tuberculosis infection	0.86	1.00	0.89, 1.00	0.43
Control	0.94	1.00	0.94, 1.00	–
2 Months of treatment				
Tuberculosis disease	0.79	0.89	0.79, 0.98	0.16
Latent tuberculosis infection	0.86	1.00	0.94, 1.00	0.16
Control	0.91	0.97	0.89, 1.00	–
4 Months of treatment				
Tuberculosis disease	0.78	0.89	0.79, 0.98	0.54
Latent tuberculosis infection	0.86	1.00	0.91, 1.00	0.51
Control	0.92	0.99	0.91, 1.00	–
6 Months of treatment				
Tuberculosis disease	0.82	0.92	0.83, 1.00	0.60
Latent tuberculosis infection	0.89	1.00	0.99, 1.00	0.67
Control	0.94	1.00	0.92, 1.00	–
9 Months of treatment				
Tuberculosis disease	0.85	0.97	0.89, 1.00	0.42
Latent tuberculosis infection	0.90	1.00	0.98, 1.00	0.49
Control	0.91	1.00	0.92, 1.00	–
12 Months of treatment				
Tuberculosis disease	0.90	1.00	0.92, 1.00	0.18
Latent tuberculosis infection	0.91	1.00	1.00, 1.00	0.21

Table 5 continued

Visit	Crude estimate	Adjusted estimate[a]	95 % confidence interval Adjusted estimate	*p* value*
Control	0.95	1.00	0.94, 1.00	–

* Indicates a *p* value less than 0.05 meaning a statistically significant difference in mean Standard Gamble health utility scores reported by the group of treated participants and the participants in the untreated control group in the adjusted model, at the given visit

[a] Adjusted models comparing participants treated for TB disease to those participants in the untreated control group controlled for age at baseline, sex, and number of individuals residing in the participants' households. Adjusted models comparing participants treated for LTBI with those participants in the untreated control group controlled for age at baseline, sex, student status at baseline (student/not a student), and participants' personal income as a percentage of total household income (participants' income as 0–19, 20–39, 40–59, 60–79, or 80–100 % of total household income)

[b] Control is a participant screened for TB who tested negative for TB and was found not to require treatment

subgroups at higher risk for TB in low-incidence settings were not properly represented in our study sample, e.g., immigrants with more limited education and/or French/English language skills, and Aboriginal peoples.

The estimates of health utility presented in this study can be used in future cost-utility analyses for a wide spectrum of TB control measures (such as improved diagnostics and new drugs or vaccines) in Montreal and potentially other urban areas in North America. As a potential alternative to disability scores derived from expert opinion, patient-derived health utility estimates from low-resource settings would be a valuable addition. These could then be applied to cost-utility analyses of TB control interventions in such settings.

Conclusion

In a diverse sample in Montreal, individuals treated for TB disease reported worse health utility within 2 weeks of diagnosis, with substantial improvement during the first months of treatment. Utility scores did not differ substantially between persons treated for LTBI and a comparable group who received no treatment, or over time for patients treated for LTBI. This suggests that for most people who continue follow-up, treatment for LTBI is associated with acceptable health utility.

These data will help reframe assessment of TB control interventions in terms of quality-adjusted survival. Our study results may be incorporated into cost-utility analyses of TB control interventions in high-resource settings.

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