Evaluating the potential costs and impact of digital health technologies for the support of tuberculosis treatment

Supplemental Methods and Sensitivity Analyses

1. Treatment Models and Details of Intervention Strategies

1.1 Strategy 1: Current Standard of Care for TB Treatment in Brazil

The following text outlines Brazilian recommendations regarding TB diagnosis and treatment. Models were based on these recommendations, with some simplifications made as described below.

TB treatment in Brazil is offered under three distinct models: self-administered treatment (SAT), community-based directly observed treatment (DOT) and health facility-based DOT. In our models, as recommended by Brazilian national authorities and according to the standard of care, persons with active TB received treatment using conventional face-to-face DOT in health facilities. In this context, active TB patients are ordinarily managed in outpatient settings from the time of diagnosis, and only patients who experience severe adverse events (SAE) or another event that does not allow outpatient treatment are hospitalized. Persons with latent TB infection (LTBI), on the other hand, follow an SAT regimen with regular clinical follow-up. Persons with LTBI are also managed in outpatient settings from diagnosis onwards, and are only hospitalized in the advent of a SAE.

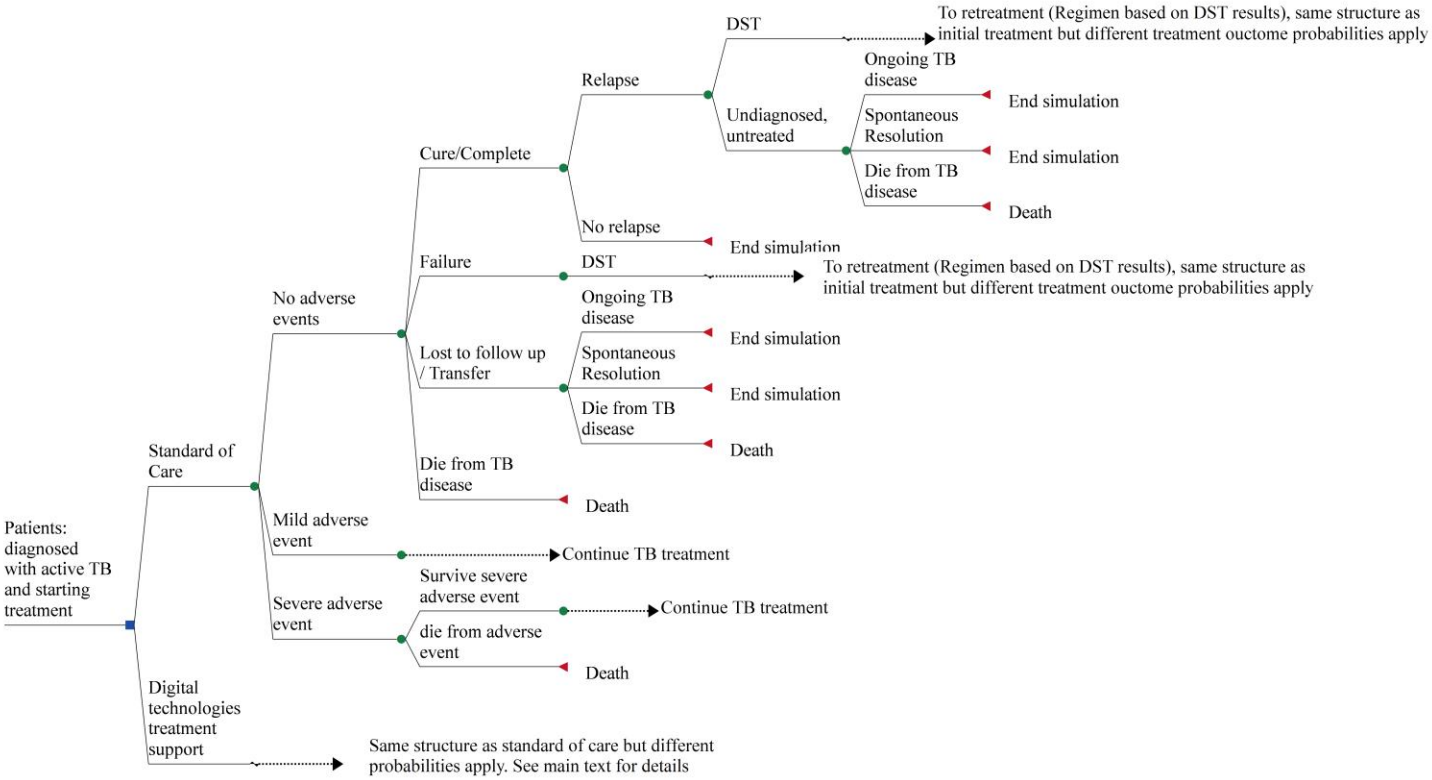
Drug-susceptible TB (DS-TB) cohort – For the DS-TB cohort, individuals were assumed to be newly diagnosed with TB, to have received no previous treatment, and to have had no contact with multidrug resistant TB (MDR-TB). Individuals were treated with a 6-month standard first-line treatment regimen. As per the Brazilian National Tuberculosis Program (NTP) guidelines, the intensive phase of treatment comprised three DOT visits per week, and the continuation phase also comprised three visits weekly, with other treatment doses unsupervised. Brazilian TB guidelines recommend a standardized rifampicin-based regimen in a fixed dose combination of Rifampicin (R), Isoniazid (H), Pyrazinamide (Z), and Ethambutol (E) taken in the intensive phase and Isoniazid (H) and Rifampicin (R) during the continuation phase (i.e. 2RHZE/4RH), summarized in Table S2 [1]. During a DOT visit, a patient undergoes supervised administration of the medication by a TB nurse. In Brazil, DOT visits are complemented by monthly clinical monitoring visits, periodic microbiology follow-up tests, and chest imaging (chest X-ray (CXR)) to evaluate response to therapy, adherence and potential adverse events (AE) [1]. Patients who experience AE receive additional test, namely a complete blood count, liver function tests (LFT), and renal function tests performed monthly. Generally, patients receive two CXRs, one during the first month of treatment and the other at the end of treatment [1]. Follow-up sputum smear microscopy is recommended every month and LFTs are obtained at the 2nd and 3rd months. Two negative smears (one during follow-up and one at the end of treatment) are required to confirm cure from TB disease. In case of a positive smear after two months of treatment, a sputum

culture is obtained with drug susceptibility testing (DST). A full cycle of DS-TB treatment is shown in Figure S1.

The Brazilian NTP recommends distinct approaches for the retreatment of TB cases who relapse after cure or complete treatment and cases who relapse after treatment failure. In retreatment of relapsed TB cases after cure or complete treatment, an Xpert MTB/RIF test, DST, and a sputum culture are done within two months, and a regimen of 2RHZE/4RH is recommended until DST results are available. In retreatment after failure, a standardized MDR-TB regimen is recommended until DST results are available (Figure S1).

For both DS- and MDR-TB, the digital interventions were assumed to replace DOT visits for observation of medication ingestion throughout treatment, but all other follow-up procedures followed the standard of care described above. Our models assumed one course of retreatment in case of failure or relapse. During treatment, patients could develop a non-severe AE or an SAE. SAEs were defined as treatment-related events resulting in hospitalization, discontinuation of treatment, and/or death [2]. For each round of treatment, we used the WHO standard treatment outcomes: treatment success (cure and/or completion); lost to follow-up (LTFU); failed, or died [3] Brazil-specific reported treatment outcomes for DS-TB are in Table S1. Patients who were LTFU, or who relapsed but were not retreated, could cure spontaneously, live with ongoing TB disease, or die. These outcomes reflected published data on the natural history of untreated TB [4, 5].

Figure S1: Simplified schematic of model structure for treatment of DS-TB. Probabilities related to each decision node are not shown. See main text for details.



MDR-TB cohort – For the MDR-TB cohort, individuals were treated with an 18-month treatment regimen. We did not consider the 9 to11 month MDR-TB regimen recommended by WHO since 2016

as it is not widely used in Brazil [6]. Multidrug resistance was defined as resistance to at least Rifampin and Isoniazid. In the Brazilian program, MDR-TB treatment involves two successive intensive phases and one continuation phase that last two months, four months and 12 months respectively. The NTP recommends at least three DOT visits weekly during the intensive phases and at least two DOT visits weekly during the continuation phase. Brazilian TB guidelines recommend *a priori* standardized treatment due to difficulties in interpretation of susceptibility results for Z, E and second line drugs. The standardized regimen includes Streptomycin (S), Ethambutol (E), Levofloxacin (L), Pyrazinamide (Z) and Terizidone (T). In both intensive phases a combination of ELTZ is taken daily for seven days and S injections are taken five days and three days a week in the 1st and 2nd intensive phases respectively. During the continuation phase a combination of ELT is taken daily for 12 months. The NTP recommends that DOT visits for MDR-TB treatment be complemented by monthly clinical monitoring visits, periodic microbiologic follow-up tests, and CXRs to evaluate response to therapy, adherence and potential AEs [1]. Monthly follow-up smear microscopy, LFT, and kidney function tests (creatinine) are recommended, and complete blood counts and sedimentation rate tests are performed every two months. CXR, sputum culture and DST are performed quarterly, and the DST is repeated in case of positive smear and/or poor radiographic response. Patients who remain smear and/or culture positive at six months must complete 24 months of treatment. Three negative smears from month 12 onwards are required to confirm cure from MDR-TB disease (i.e. negative cultures at months 12, 15 and 18), we reclassified data from SINAN, the comprehensive Brazilian disease database, to fit WHO standard treatment outcomes for patients with confirmed MDR-TB and who started treatment between 2010 - 2012 (Table S1). If the 12-month culture was positive, cure was defined by four negative cultures without clinical or radiological signs of continuing disease until the 24th month (i.e. negative culture at months 15, 18, 21 and 24). According to the guidelines, retreatment of relapsed cases or cases who failed treatment begins with an Xpert MTB/RIF test, DST, and culture.

Table S1: TB treatment outcomes, Brazil

	TB patients (2013-2014) [a]		MDR-TB (2010-2012) [b]	
Outcomes *	**Previously untreated (assumed to be DS) (n = 140,125)**	**Retreatment confirmed DS (n = 26,574)**	**New (n = 1,632)**	**Retreatment (n = 327)**
Treatment success	73%	49%	67%	25%
LTFU	19%	39%	18%	34%
Failure	0.1%	3%	6%	16%
Death	8%	8%	10%	25%

[a] Standard treatment outcome for all new and retreatment patients started on treatment in 2013 and 2014, calculated using data from SINAN database
[b] MDR-TB treatment outcomes for patients who were confirmed MDR and started treatment between 2010-2012
LTFU: Lost to follow-up, DS: Drug-susceptible
* SINAN outcome categories were classified under WHO treatment outcomes as follows:
- Treatment success = cure (Cura)
- LTFU = Default + primary default + transfer + not evaluated (Abandono + Abandono Primário + Transferência + Ign/Branco)
- Failure = Drug resistant TB + failure + treatment change (TB-DR + Falência + Mudança de Esquema)
- Death = TB related death + death from other causes (Óbito por tuberculose + Óbito por outras causas)

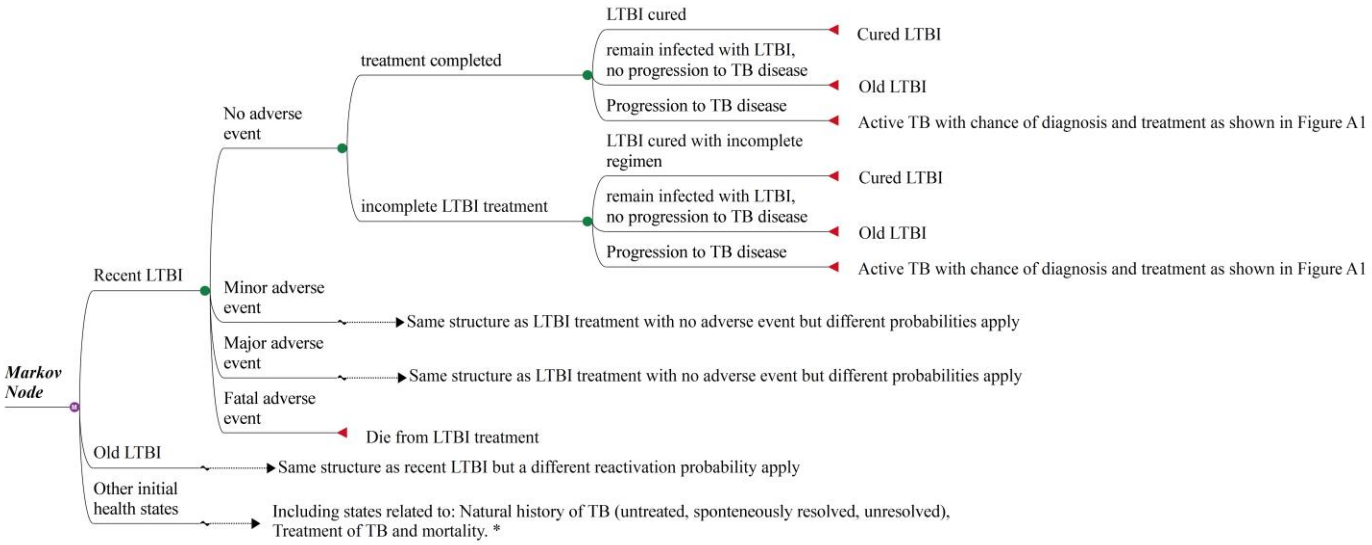
Table S2: Treatment regimens for DS-TB, MDR-TB, and LTBI

Treatment regimen	Daily dose (>50kg)		Duration	Daily/weekly cost	Overall cost	Reference
DS-TB Regimen						
2RHZE (intensive phase)	Rifampin Isoniazid Pyrazinamide Ethambutol	600 mg 300 mg 1,600 mg 1,100 mg	2 months	$0.238/day	$14.50	[7]
4RH (regular maintenance phase)	Rifampin Isoniazid	600 mg 300 mg	4 months	$0.112/day	$13.67	[7]
7RH (extended continuation phase)	Rifampin Isoniazid	600 mg 300 mg	7 months	$0.112/day	$23.92	[7]
Total cost for 6-months DS-TB drugs **Total cost for 9-months DS-TB dugs**					**$28** **$38**	
MDR-TB Regimen						
$2S_5ELTZ$ (1st intensive phase)	Streptomycin Ethambutol Levofloxacin Terizidone Pyrazinamide	1000 mg 1200 mg 750 mg 1000 mg 1500 mg	2 months	$101.09/week	$887	[7]
$4S_3ELTZ$ (2nd intensive phase)	Streptomycin Ethambutol Levofloxacin Terizidone Pyrazinamide	1000 mg 1200 mg 750 mg 1000 mg 1500 mg	4 months	$101.09/week	$1,752	[7]
12ELT (regular continuation phase)	Ethambutol Levofloxacin Terizidone	1200 mg 750 mg 1000 mg	12 months	$98.99/week	$5,148	[7]
18ELT (extended continuation phase)	Ethambutol Levofloxacin Terizidone	1200 mg 750 mg 1000 mg	18 months	$98.99/week	$7,721	[7]
Total cost for 18-months MDR-TB drugs **Total cost for 24-months MDR-TB drugs**					**$7,787** **$10,361**	
LTBI Regimen						
9-months INH	Isoniazid	300 mg	9 months	$0.019/day	$5.20	[7]
3-months INH	Isoniazid	300 mg	3 months	$0.019/day	$1.73	[7]
Total cost for 9-months LTBI drugs					**$5.20**	
Total cost for incomplete 3-months (interrupted) LTBI drugs					**$1.73**	

LTBI cohort – Individuals in the LTBI cohort were assumed to be infected with INH/RIF susceptible TB, without previous treatment for LTBI or TB. The Brazilian NTP recommends using a 9-month Isoniazid (INH) regimen for LTBI. In our models, SAT, the current standard of care for LTBI treatment in Brazil, was compared with digital interventions for treatment support. While these were assumed to replace SAT, all subsequent clinical follow-up procedures followed the Brazilian National TB Program guidelines [8]. During LTBI treatment, persons could develop non-severe, severe, or fatal adverse events, which could lead to treatment interruption, hospitalization, and/or death. Those who developed active TB disease were eligible for diagnosis and a 6-month standard treatment regimen, using DOT as part of standard care.

The Brazilian NTP recommends monthly clinical monitoring visits during LTBI treatment, to evaluate adherence and potential AE [1, 9]. Persons who experience an AE receive at least one additional medical visit and two supplemental complete blood counts and liver enzyme blood tests, as well as any further care appropriate to the severity of their event. A simplified schematic of the LTBI model is shown in Figure S2.

Figure S2: Simplified schematic of the Markov model structure for LTBI treatment. Probabilities related to each decision node are not shown. See main text for details.



*The detailed structure is not shown in order to simplify the model

1.2 Strategy 2: Digital Health interventions

Medication Monitors (MM)

We considered two MM strategies: one involving a medication dispenser (Wisepill®) and the other using custom envelopes with toll free numbers (99DOTS®). Wisepill combines SMS with an electronic monitor attached to a standard medication dispenser [10-17]. The device sends an SMS to a web-based application each time the bottle is opened. If a scheduled dose is missed in the window period pre-set by the health care professional, a text message is sent to the patient as a reminder and to the treatment team for adherence support. 99DOTS uses blister packs wrapped in custom envelopes with hidden toll free numbers that are only revealed after each medication dose is removed from the pack. The patient calls the toll-free number to signal the dose has been taken.

In the LTBI model, the effect of MM on treatment completion was calculated using published data from a randomized trial that evaluated this technology in TB care in China. [18, 19] The trial reported cluster geometric means of the percentage of patients-months on TB treatment where at least 20% of doses were missed. In the control arm, 29.9% of patient-months had at least 20% of doses missed, whereas in the medication monitor arm, 17.0% of patients-months did. In order to obtain an estimate of effect comparable to those reported for the other interventions in our models, we calculated a relative risk (RR) of treatment completion for MM compared to SAT using published data from the trial.

In the LTBI model, we assumed that the effect of MM on missing doses was complementary to an effect on improved treatment completion (i.e., patients who were less likely to miss doses were assumed to be more likely to complete treatment). Because 29.9% of patient-months had 20% or more missed doses in the control arm, conversely, we assumed treatment was completed (more than

80% of doses taken) in 70.1% of patient-months observed. Similarly, 17.0% of patient-months had 20% or more missed doses in the MM arm, and treatment was assumed to be completed in 83.0% of patient-months observed. Thus:

$$RR_{completion} = \frac{\%\ patient\ months\ of\ completed\ treatment, MM}{\%\ patient\ months\ of\ completed\ treatment, control} = \frac{83.0\%}{70.1\%} = 1.18$$

Analogous calculations were repeated using the confidence intervals published in the trial. Although patient-months were used in the trial to compare treatment regiments of different durations, our models took this RR to be applicable to an entire round of treatment (regardless of length). Thus, the modeled RR of treatment completion was 1.18 (95% CI 1.08-1.26), comparing MM to SAT.

Video-observed treatment (VOT)

In the context of active TB, the VOT intervention involved replacing routine in-person DOT visits with video calls that lasted approximately 5 minutes (range 4 to 7) [20]. In the context of LTBI, video calls replaced SAT. During the video session the nurse made enquiries about side effects and, if none were present, the patient was asked to name and show the pill to the camera before swallowing it [21]. VOT sessions were considered successful if a patient was observed ingesting the full dose of prescribed medication on scheduled days and times [21].

Two-way short message service (SMS) [LTBI only]

We operationalized the two-way SMS intervention using an approach proposed in British Columbia in 2014, and informed our model with data from a meta-analysis of text messaging interventions in different disease settings [22, 23]. Weekly text-message “check-ins” were sent from an automated, central computer, asking the patient: “Are you OK? Have you taken your tuberculosis medication?” Patients were asked to respond within 48 hours, by answering “Yes” or “No”. A TB clinic nurse reviewed all incoming SMS messages that differed from “Yes” on the clinic computer and addressed any identified problems. First instances of non-response resulted in a second text sent to the patients, who once more had 48 hours to respond. If the patient did not answer this second text message, the TB clinic nurse followed-up by phone. Text messages were sent weekly throughout the full course of treatment, or until treatment interruption. This SMS intervention supplemented, but did not replace, existing clinical protocols [24]. Two-way SMS was not considered for active TB cases as two randomized trials have shown this approach to have no effect on adherence to treatment in active TB patients. [18, 19]. Because LTBI therapy is not directly observed and may therefore more closely resemble antiretroviral-based HIV care, measures of effect for the two-way SMS intervention were obtained from the largest published trial of two-way SMS versus SAT in HIV. The modeled RR of treatment completion was 1.24 (95% CI 1.06-1.45), comparing SMS to SAT [25].

1.3 Model inputs and key assumptions:

Tuberculosis Pathogenesis and Treatment

DS-TB – Published literature on the natural history of TB estimates that 25% of cases with untreated TB disease spontaneously resolve [4] and 19% will die from untreated TB [5]. We assigned the same probabilities to patients who were untreated after LTFU or relapse. The relapse rate used was 3.8% (adapted from [26]). Based on Brazil's TB case detection rate of 87%, we assumed that 87% of relapsed cases would be retreated [27]. We assumed that 100% of patients with treatment failure would be retreated, and that patients who were retreated after initial treatment failure had a higher probability of resistance to anti-TB drugs (75%) including MDR, than patients who relapsed after successful treatment (17.4%) (adapted from [28]). Treatment outcomes were obtained from SINAN.

MDR-TB –We assumed the natural history of untreated TB to be the same for all active TB cohorts. The relapse rate after successful MDR-TB treatment was 14% (adapted from [26]).

LTBI – In the cohort of close contacts of active TB, 82% were assumed to have been infected in the last 2 years, and the remainder of the cohort was taken to have long standing infection, based on an assumed age of 35 years for cohort members and annual risk of infection of 0.54%. In the unselected general population cohort, 5.7% of individuals with LTBI were assumed to have acquired infection within two years prior to the start of the simulation; the remainder of the cohort was assumed to have long-standing LTBI infection. Those who were recently infected experienced a higher rate of progression to incident active TB, while those with long-standing infection reactivate at a much lower rate.

Treatment completion rates were assumed to vary depending on the occurrence of AE (see next section). 90% of those completing the full treatment regimen were assumed to be cured [29, 30]. We further assumed that persons who did not complete the 9-month regimen interrupted their treatment after 101 days, which was the reported median time until the onset of treatment-limiting hepatotoxicity in a major longitudinal study [31]. A course of isoniazid similar in length to this interrupted regimen has been shown to reduce the probability of subsequent active TB by 21% [30]. The probability of recent LTBI progressing to active TB disease was 5% over two years [32, 33], and the yearly probability of long-standing LTBI reactivation 0.1% [34, 35]. Incident TB cases were assumed to be diagnosed at the 2016 Brazilian case-detection rate [27], and treatment initiation for active TB after diagnosis of incident TB in Brazil was 87% [36]. The natural history of active TB, as well as active TB treatment and retreatment outcomes, were the same as described above for the DS-TB model.

Adverse Events

DS-TB cohort – We assumed that the presence of SAEs would prolong active TB treatment from six to nine months. The assumption of extended treatment was based on the NTP guidelines for managing SAEs which involves discontinuation of TB treatment and then switching anti-TB medications while simultaneously treating AEs [1]. Assumptions related to AE treatment and hospitalization rates were based on a published report of at least 3-week duration for all AEs [37].

Based on this study, 5% of DS-TB patients were assumed to experience an AE [38] and 10% of these AEs were severe enough to require a one-week hospitalization.

MDR-TB cohort – The presence of SAEs was assumed to prolong the treatment period for in-person DOT from 18 months to 24 months based on the same AE management guidelines [1]. Pooran et al. reported that 30% of MDR-TB patients experienced at least one AE [37, 39] and that 30% of these were severe enough to lead to a two-week long hospitalization.

LTBI cohort – Fatal AEs were defined as those resulting in death during the 9-month care period. Severe AE involved hematologic problems, hepatotoxicity, or drug hypersensitivity, and non-severe AE were defined as gastrointestinal disturbances, fatigue, dizziness, rashes and dermatologic issues, and other side effects. Risks of fatal, severe, and non-severe AE were calculated from a major network meta-analysis by Stagg et al., and were respectively 0.0068%, 2.7%, and 3.6%. [40] Rates of treatment completion after severe, non-severe, and no AE were calculated from the literature [41-43]: respectively 17.4%, 55.4%, and 65.7%. We assumed that persons who ultimately died following an AE would have on average two consultations with medical specialists and one week of hospitalization. Among those with a severe AE, we assumed all would require two further consultations with medical specialists, but only some would need hospitalization. Data from Stagg et al. and Smith et al. suggested than 48.9% of the patients with severe AE would require one week of hospitalization [40, 44].

Table S3a. Model parameters related to the natural history, epidemiology, and treatment of LTBI and TB

	Value	Range or SD	Reference
Pathogenesis, natural history, and epidemiology			
Probability of spontaneous resolution of untreated TB disease	25%		[4]
Probability of relapse following spontaneously resolved TB	2.5%		[4, 45]
Probability of relapse after cured MDR-TB disease in first year	14%		[26]
Probability of dying from untreated TB (per year)	19%		[5, 46]
Probability of relapse after cured DS-TB disease in first year	3.8%		[26]
Probability of spontaneous cure after partial TB treatment	62%		[47, 48]
Probability of progression of recently acquired LTBI to TB disease	5%	(2-15)	[32, 33]
Probability of reactivation of old-standing LTBI to TB disease (per year)	0.1%	(0.1-0.2)	[34, 35]
Probability of detecting a case of active TB (case-detection), Brazil	87%	(75-100)	[49]
Probability of acquiring resistance, after failed initial TB treatment	75%		[28]
Probability of acquiring resistance, given relapsed TB after successful treatment	17%		[28]
LTBI Treatment			
Efficacy of complete 9-month INH regimen, INH sensitive	90%		[29, 30]
Efficacy of incomplete INH regimen, INH sensitive [a]	21%		[30]
Probability of completing LTBI treatment, no technological support	62%		[50]
Assumed probability of completing LTBI treatment, two-way SMS	77%		[50, 51]
Assumed probability of completing LTBI treatment, VOT	73%		[18, 50]
Assumed probability of completing LTBI treatment, MM	73%		[18, 50]
Adverse reactions			
Probability of having non-severe adverse event while taking initial TB regimen	10%	(1.24)	[52]
Probability of having severe adverse event while taking initial TB regimen	2%	(0.69)	[52]
Probability of having non-severe adverse events while taking MDR-TB regimen	25%		[53, 54]
Probability of developing severe adverse event while taking MDR-TB regimen	32%		[54]
Risk of death, given severe adverse event while taking initial or MDR-TB regimen	0.68%		[40]
Probability of having non-severe adverse event from LTBI treatment	3.6%		[40]
Probability of having severe adverse event from LTBI treatment	2.7%		[40, 55]
Probability of having fatal adverse event from LTBI treatment	0.0068%		[40]

SD: Standard deviation, INH: isoniazid.

a Data from the PREVENT TB trial suggest that treatment interruption due to adverse events occurred after a median time of 97-105 days. [31] In our models, when necessary, treatment was assumed to be interrupted just over 3 months into the regimen. A 12-week INH regimen has been shown to lead to a 21% reduction in risk of developing active TB. [30] We assume that 3 months of INH will be efficacious in the treatment of LTBI in 21% of patients.

Disability-adjusted life years (DALYs)

Years lived with disability (YLD) and years of life lost due to premature mortality (YLL) were used to calculate DALYS (YLD+YLL). The same disability weight was applied to both DS-TB and MDR-TB. However, we assumed that those undergoing treatment for DS-TB would only experience disability for the duration of their six-month treatment regimen, and thus the yearly disability weight would be half (0.1655) of that reported for a full year (0.331) with untreated active TB [56]. Persons with LTBI are asymptomatic and therefore do not contribute DALYs to our calculations, unless they die from an LTBI treatment-related AE.

We defined YLD as the duration of time on TB treatment or time with TB before death multiplied by the disability weight. YLL was defined as remaining life expectancy at the age of death (assuming a start age of 35). DALYs lost in future years were discounted at 3%.

Table S3b: Disability-adjusted life year weights for drug sensitive and MDR-TB in Brazil

	Value	Range	Reference
DALY weight for active TB (Untreated TBD)	0.331	(0.224-0.454)	[57]
DALY weight for active TB (Treated TBD)	0.1655	(0.112-0.227) [§]	[56, 57]
Life expectancy at age 35, Brazil (years)	42.4		[58]

[§] assumes that TB treatment results in 50% reduction in disability relative to those with untreated active TB [56], DALY: disability-adjusted life years

Costs

Detailed costs and sources are detailed in Tables S4-S9.

Health system Costs – To supplement cost data available in the published literature, hospitalization costs were obtained from Brazil's Ministry of Health [59], medication costs were obtained from the Global Drug Facility [7] and the cost of mobile phone and data packages was obtained from Brazilian phone companies [60].

Table S4: Per person health system costs for diagnosis and treatment of drug-susceptible TB , Brazilian standard of care

	Value	Range or SD	Reference
TB Pre-Diagnosis			
Cost of medical Consultation: initial assessment	$14.93	(7.47-29.87)	[61]
Cost of Complementary exams	$3.46	(11.51)	[62]
Subtotal - Pre-Diagnosis	*$18.39*		
Standard Initial tests for diagnosis			
Cost per CXR	$14.13	(7.06-28.26)	[61]
Cost per Xpert MTB/RIF	$14.93	(7.47-29.87)	[61]
Prorated cost of Culture (for Xpert negative high suspicion) [u]	$1.13		[61]
Total Diagnostic cost	*30.19*		
Treatment and Follow up			
Fixed-dose combination 2RHZE/4RH (6-months regimen)	$28.17		[7]
Fixed-dose combination 2RHZE/7RH (9-months regimen)	$38.42		[7]
Hospitalization for 24 days (pro-rated at 5.19 per day per TB case)	$124.70		[59]
Cost per DOT visit	$8.45		[62]
Subtotal - DOT visits (regular treatment: 61 visits)	*$512.63*		[1, 61]***
Subtotal - DOT visits (extended treatment: 87 visits)	*$732.33*		[1]
Cost per Follow-up visit with medical doctor	$14.86	(7.43-29.73)	[61]
Subtotal - Follow-up visit (regular treatment: 6 visits)	*$89.18*		
Subtotal - Follow-up visit (extended treatment: 9 visits)	*$133.77*		
Cost per sputum smear (per sample)	$3.13	(0.89-6.25)	[61]
Cost per Liver Function Test	$3.79	(1.88-7.50)	[9]
Subtotal - Follow-up lab/tests (regular treatment: 3 smears and 1 LFT)	*$13.17*		
Subtotal - Follow-up lab/tests (extended treatment: 4 smears and 2 LFTs)	*$20.08*		
CXR, during treatment (2 done)	$28.26		[61]
Treatment and Follow up – Regular 6-months treatment	*$796.11*		
Treatment and Follow up – extended 9-months treatment	*$1,077.57*		
Grand total per person – pre-diagnosis, standard diagnosis and treatment follow up (6-months)	**$845**		
Grand total per person– pre-diagnosis, standard diagnosis and treatment follow up (9-months)	**$1,126**		

[u] From Brazilian TB guidelines, culture is only done when there is high clinical suspicion but Xpert result is negative
**Pre-diagnostic and Diagnosis costs applied only to incident active cases or relapse cases who are subsequently retreated. Treatment and follow up costs applied to all active cases.
*** Calculated inputs from listed publications

Table S5: Per person health system costs for diagnosis and treatment of LTBI, Brazilian standard of care

Parameter	Value	Range	Reference
a) Cost of initial visit, total (nurse + MD)	$ 4.75	(2.37-9.49)	[9]
b) Cost/dose of 9H, dose (daily)	$ 0.019		[7]
c) Number of Follow-up visits	9		
d) Cost of a single follow-up visit, (nurse + MD)	$ 4.75	(2.37-9.49)	[9]
Total cost – Complete 9-months treatment (a + b*9months daily doses + c*d)	*$52.70*		
Total cost – Complete 3-months treatment (a + b*3months daily doses + 3*d)	*$22.44*		
Grand total per person – standard diagnosis and treatment follow up (9-months)	**$53**		
Grand total per person – standard diagnosis and treatment follow up (3-months)	**$22**		

Table S6: Per person Health system costs for MDR-TB diagnosis and treatment, Brazilian standard of care

Parameter	Value	Range	Reference
a) Sub-total for pre-diagnosis and initial diagnostic testing (standard +additional)	*$48.58*		*Table S4 above*
Treatment and Follow up			
b) Fixed-dose combination: $2S_5ELTZ$ (18-months regimen)	$7,786.99		[7]
c) Fixed-dose combination: $2S_5ELTZ$ (24-months regimen)	$10,360.76		[7]
d) Hospitalization for 24 days (prorated per TB case)	$124.70		[59]
e) DOT visits (regular treatment: 182 visits)	$1,537.90		[1, 61]***
f) DOT visits (extended treatment: 234 visits)	$1,977.30		[1, 61]***
g) Follow-up consultation (regular treatment: 18 visits)	$267.54		[61]
h) Follow-up consultation (extended treatment: 24 visits)	$356.64		[61]
i) Cost per Culture	$8.37	(4.18-16.73)	[61]
j) Cost for a complete blood count (CBC)	$2.58	(1.29-5.16)	[9]
k) Follow-up lab/tests (regular treatment: 18 smears, 6 cultures, 9 CBC and 9 LFT)	*$163.8*		
l) Follow-up lab/tests (extended treatment: 24 smears, 8 cultures, 12 CBC & 12 LFTs)	*$218.4*		
m) CXR (regular treatment: 6 done)	$84.78		[61]
n) CXR (extended treatment: 8 done)	$113.04		[61]
Total cost – regular 18-months treatment (b + d + e + g + k + m)	*$9,965.71*		
Total cost – extended 24-months treatment (c + d + f + h + l + n)	*$13,150.92*		
Grand total per person– pre-diagnosis (a), standard diagnosis and treatment follow up (18-months)	**$10,014**		
Grand total per person – pre-diagnosis (a), standard diagnosis and treatment follow up (24-months)	**$13,200**		

**Pre-diagnostic and Diagnosis costs applied only to incident active cases or relapse cases who are subsequently retreated. Treatment and follow up costs applied to all active cases.

*** Calculated inputs from given publications

Table S7: Per person health system costs for DS-TB and MDR-TB re-treatment, Brazilian standard of care

	Value	Ref.
Subtotal - for pre-diagnosis (Table S4 for DS-TB above) [h]	*$18.39*	*Table S4 above*
Cost per Xpert MTB/RIF	$14.93	[61]
Cost of Drug susceptibility testing (1 sample)	*$ 19.81*	[61]
Cost per CXR	$14.13	[61]
Cost per Culture	$8.37	[61]
Subtotal - for additional tests: Xpert, DST, CXR and culture	*$57.24*	
Grand totals per person - Pre-diagnosis [h], Diagnosis, Treatment and FU according to DST results		
Relapse after DS-TB treatment: DST indicates drug sensitive: taking 6-m DS-TB regimen)	**$872**	
Relapse after DS-TB treatment: DST indicates resistance: taking (2-m DS-TB) + (18-m MDR-TB regimen)	**$10,326**	
Failure of DS-TB treatment: DST indicates drug sensitive: taking (2-m MDR-TB) + (4-m DS-TB regimen)	**$1,718**	
Failure of DS-TB treatment: DST indicates drug sensitive: taking (18-m MDR-TB regimen)	**$10,023**	
Relapse after MDR-TB treatment: (18-m MDR-TB regimen)	**$10,041**	
Failure of MDR-TB treatment: (18-m MDR-TB regimen)	**$10,023**	

[h] Costs associated with pre-diagnosis are only applied to relapse cases, and not to failure cases as all are retreated without delay

Patient Costs – Direct and indirect patient costs (Table S8) were obtained from a study of TB costs in Brazil by Steffen et al. [62] This study compared costs for patients undergoing in person DOT vs SAT. The study reported all direct and indirect costs during different phases of TB illness incurred by patients and their families [62]. Since digital technologies would eliminate DOT visits during treatment, we assumed that patient costs after diagnosis for patients receiving treatment with digital technology support were equivalent to previously reported patient costs for self-administered treatment [63].

Table S8: Per person Direct and indirect patient costs in the treatment of drug-susceptible TB, MDR-TB and LTBI in Brazil

	Value* **	**Range or SD**	**Reference**
Direct costs			
Before TB diagnosis	$32.63	(42.39)	[62]
6-month Treatment follow up period (excluding hospitalization) (standard of care- DOT)	$129.96	(416.02)	[62]
6-month Treatment follow up period (excluding hospitalization) (digital technology*)	$41.83	(61.90)	[62]
Hospitalization for 24 days (pro-rated at $0.30 per day per TB case)	$6.26	(33.78)	[62]
Per day Cost of AE related hospitalization	$1.93		[62]
Indirect costs			
Before TB diagnosis	$50.57	(205.88)	[62]
6-month Treatment follow-up period (excluding hospitalization) (standard of care DOT)	$127.83	(366.34)	[62]
6-month Treatment follow-up period (excluding hospitalization) (digital technology*)	$56.74	(64.36)	[62]
Hospitalization for 24 days (pro-rated at $1.44 per day per TB case)	$29.87		[62]
Per day Cost of AE related hospitalization	$9.17		[62]
Digital tech. related training costs	**$0.24**		
Declared income per hour	$1.9	(1.5–3.2)	[63]
Patient training duration (in min)	7.5	(5-10)	
LTBI Patient costs			
Total patient costs, SAT, no hospitalization, per 6 months of treatment	$98.33	(89.05)	[62]
Per Person Cost of pre-diagnosis, diagnosis, treatment FU and hospitalization	**DOT/SAT**	**Digital tech.** U	
direct cost – regular 6-months	*$137*	*$49*	
direct cost – extended 9-months	*$215*	*$83*	
direct cost – regular MDR-TB 18-months	*$396*	*$132*	
direct cost – extended MDR-TB 24-months	*$553*	*$201*	
indirect cost – regular 6-months	*$162*	*$91*	
indirect cost – extended 9-months	*$290*	*$184*	
indirect cost – regular MDR-TB 18-months	*$417*	*$205*	
indirect cost – extended MDR-TB 24-months	*$673*	*$390*	
digital tech. related training costs		*$0.24*	
Total patient cost (direct + indirect): Drug-susceptible 6-months treatment	**$299**	**$140**	
Total patient cost (direct + indirect): Drug-susceptible 9-months treatment	**$505**	**$267**	
Total patient cost (direct + indirect): MDR-TB 18-months treatment	**$813**	**$337**	
Total patient cost (direct + indirect): MDR-TB 24-months treatment	**$1,226**	**$591**	
Total patient cost: Incomplete LTBI 3-months treatment	**$49**[#]	**$49**	
Total patient cost: Complete LTBI 9-months treatment	**$148**[#]	**$148**	

Indirect costs calculated using time spent, converted to currency using assumed hourly wage and mean GDP in Brazil in 2008 adjusted for inflation in 2016.

*assume equivalent patient costs to those incurred under self-administered treatment

**Pre-diagnostic and diagnosis costs applied only to incident active cases or relapse cases who are subsequently retreated. Treatment and follow up costs applied to full initial cohort of active cases.

*** Calculated inputs from [62]

[#] LTBI treatment model is SAT

[u] We add $0.24 training costs for digital technologies

Technology Costs – VOT costs included smartphones lent to patients who did not already own them, SIM cards, video calls data, and TB clinician wages and training related to the technology use. Costs for the Wisepill® MM intervention included medication dispensers, monthly data monitoring, data hosting fees and intervention specific follow-up costs. 99DOTS® costs included annual rental of toll free lines, envelopes and SMS and follow up calls. Patient costs related to technology training were calculated based on declared income per hour in Brazil reported by Trajman et al. [63]. These aggregate costs do not include component costs related to treatment (Table S9)

Table S9a: Per person Technology costs for Wisepill® medication monitor intervention [u]

		Value	Range	Reference
Medication monitors -Wisepill®				
a)	Electronic drug monitor (MM): Wisepill dispenser - RM1000	$22.5		[64]
b)	Sim Card	$3.06		[60, 65]
c)	Monthly data monitoring and hosting fee	$1		[64]
d)	Airtime to transmit data for 3 months	$0.80		[12]
Follow-up costs in case of non-adherence				
e)	Proportion of patients who do not open MM, despite SMS reminder	0.2743		***
f)	Proportion of patients who do not open MM due to other reasons (e.g. AE)	0.1239		[52]****
g)	HCW time required to respond to call patient who does open MM (min)	3		[66]
h)	HCW time required to respond to patient with a problem (min)	20		[67]
i)	Mean, weighted HCW time/patient (min) (e*g + f*h)	2.3782		
j)	TB nurse wage/minute	$0.157		[67]
k)	*Subtotal – Intervention-specific FU cost (to be added to all patients) (i*j)*	*$0.518*		
l)	Mean nurse training cost (pro-rated per TB case)	$1.93		
m)	Intervention-specific FU cost (to be added to all LTBI patients)	$0.37		
n)	Mean prorated nurse training cost (to be added to all LTBI-patients)	$0.56		
Per person total:				
Drug-susceptible 6-months treatment support [a + b + 6*(c +d/3) + k + l]		**$36**		
Drug-susceptible 9-months treatment [a + b + 9*(c +d/3) + k + l		**$39**		
MDR-TB 18-months treatment [a + b + 18*(c +d/3) + k + l]		**$51**		
MDR-TB 24-months treatment [a + b + 24*(c +d/3) + k + l]		**$58**		
Complete 9-months LTBI treatment support [a + b + 9*(c +d/3) + m + n		**$38**		
Incomplete 3-months LTBI treatment support [a + b + 3*(c +d/3) + m + n		**$30**		

Table S9b: Technology costs for 99DOTS® medication monitor intervention [u]

		Value	Range	Reference
Medication monitors -99DOTS®				
a)	Fixed cost of renting a toll-free line per patient in a year	$0.035		[68]
b)	Cost of envelopes (including secondary packaging, labels, and shipping)	$2.34		[68]
c)	SMS and call costs (assuming high adherence over treatment course)	$2.47		[68]
d)	Cost of labor to wrap medication (worst case scenario)	$0.20		[68]
e)	Mean nurse training cost (pro-rated per TB case)	$1.93		
f)	Subtotal – Intervention-specific FU cost (to be added to all patients)	*$0.518*		
g)	Intervention-specific FU cost (to be added to all LTBI patients)	$0.37		
h)	Mean prorated nurse training cost (to be added to all LTBI-patients)	$0.56		
Per person total:				
Drug-susceptible 6-months treatment [a + b + c + d + e + f]		**$7**		

Drug-susceptible 9-months treatment [a + 9/6(b + c + d) + e + f]	**$10**
MDR-TB 18-months treatment [2*a + 3(b + c + d) + e + f]	**$18**
MDR-TB 24-months treatment [2*a + 4(b + c + d) + e + f]	**$23**
Complete 9-months LTBI treatment support [a + 9/6(b + c + d) + g + h]	**$8**
Incomplete 3-months LTBI treatment support [a + 1/2(b + c + d) + g + h]	**$3**

Table S9c: Per person Technology costs for video-observed treatment intervention[υ]

	Value	Range	Reference
VOT			
a) Weighted cost of smartphones (for 59% of patients who do not own one)	$54.08		[60]
b) Weighted cost of a SIM card (for 59% of patients who do not own one)	$1.80		[60, 65]
c) Video call megabytes (MB) use per minute	3		[69]
d) Daily package: $/1 MB [æ]	$0.02		[60]
Average number of minutes per call	5.3	(4.0-6.6)	[20]
e) Total Internet/data package required for DS-TB - VOT (6 months)	*1240.20MB*		
f) Total Internet/data package required for DS-TB - VOT (9 months)	*1653.56MB*		
g) Total Internet/data package required for MDR-VOT (18 months)	*3720.60MB*		
h) Total Internet/data package required for MDR-VOT (24 months)	*4547.40MB*		
TB nurse wage/minute	$0.16		[67]
i) Total nurse VOT Cost per patient - DS-TBD - 6 months	*$64.90*		
j) Total nurse VOT Cost per patient - DS-TBD - 9 months	*$86.54*		
k) Total nurse VOT Cost per patient - MDR-TBD - 18 months	*$194.71*		
l) Total nurse VOT Cost per patient - MDR-TBD - 24 months	*$237.98*		
m) Mean nurse training cost (pro-rated per TB case)	$1.93		
LTBI			
n) Total Internet/data package required for LTBI-VOT (MB/9 months)	*3100.50MB*		
o) Total Internet/data package required for LTBI-VOT (MB/3 months)	*1033.50MB*		
p) Total nurse VOT Cost per patient – LTBI 9 months	*$86.54*		
q) Total nurse VOT Cost per patient – LTBI 3 months	*$54.09*		
r) Mean prorated nurse training cost (to be added to all LTBI-patients)	*$0.56*		
Per person total:			
Drug-susceptible 6-months treatment [a + b + 2(d*e) + i + m]	**$173**		
Drug-susceptible 9-months treatment [a + b + 2(d*f) + j + m]	**$211**		
MDR-TB 18-months treatment [a + b + 2(d*g) + k + m]	**$403**		
MDR-TB 24-months treatment [a + b + 2(d*h) + l + m]	**$479**		
Complete 9-months LTBI treatment support [a + b + 2(d*n) + p + r]	**$344**		
Incomplete 3-months LTBI treatment support [a + b + 2(d*o) + q + r]	**$152**		

[υ] all other costs shown in Tables S4 and S6 EXCEPT DOT visit costs apply to active TB cases in digital technology scenarios. These aggregate costs do not include cost components related to treatment. [h] Brazil has approximately 70,000 new active TB cases per year. Assuming 4 contacts per case, we assumed that 280,000 contacts per year would receive treatment in 4,745 TB clinics (Oliveira (2013))

[æ] Cost of data doubled since the health system would pay for data consumption for both the nurse and the patient *** Assumption: equivalent to compliment of completed treatment (calculated using data from SINAN database) **** Assumption: equivalent to total AE rates for TB disease (calculated using data from Gallardo (2016))

2. Sensitivity analyses

Univariate – One-way sensitivity analyses were performed for each of the three cohorts (DS-TB, MDR-TB, LTBI) by creating tornado diagrams to identify parameters with the greatest influence on total projected costs, and on incremental costs per TB case averted and per DALY averted in the case of LTBI. Parameters were varied using their published minimum and maximum values.

Threshold analysis – In the LTBI model, threshold analyses were performed to identify the minimal efficacy of intervention required to ensure cost-effectiveness with respect to DALYs averted. For all interventions, the threshold for cost-effectiveness was an estimated incremental cost per DALY averted that was less than the 2016 Brazilian per capita GDP, i.e. $8,650 US.

Probabilistic Sensitivity Analysis (PSA) – A PSA was conducted with 10,000 Monte Carlo trials to obtain 95% uncertainty ranges (UR) (2.5^{th} and 97.5^{th} percentiles) around point estimates for outcomes. We defined distributions for all variables based on published or calculated ranges and standard deviations (Table S10). For treatment outcomes obtained from SINAN, 95% confidence intervals were calculated using binomial distributions; we used their means and standard deviations to calculate alpha and beta values when fitting beta distributions used in the model. For other parameters, beta distributions were fitted to 95% confidence intervals obtained from published data. For costs, DALY weights, and relative risks, triangular distributions fitted to their lower and upper limits were obtained from the literature. We used acceptability curves to show the probability of cost-effectiveness of each intervention against the threshold value.

Table S10: Distributions and ranges of probability and cost variables used in sensitivity analyses

Model	Variable description by category	Distribution	Expected Value
Active TB	Adjusted mean ratio for months with 20% or more missed doses	Triangular	0.59 (min: 0.42, likeliest: 0.58, max: 0.79)
LTBI	Distribution of MR (effect) for medical monitor	Triangular	1.17 (min: 1.08, likeliest: 1.18, max: 1.26)
LTBI	Distribution of MR (effect) for VOT intervention	Triangular	1.17 (min: 1.08, likeliest: 1.18, max: 1.26)
LTBI	Distribution of risk ratio for SMS intervention	Triangular	1.24 (min: 1.06, likeliest: 1.24, max: 1.45)
	Health system costs		
LTBI & Active TB	Average number of minutes per call	Triangular	5.3 (min: 3.975, likeliest: 5.3, max: 6.625)
LTBI & Active TB	Cost for a complete blood count (CBC)	Triangular	$3.01 (min: 1.29, likeliest: 2.58, max: 5.16)
LTBI & Active TB	Cost of daily DS-TB meds: RH (maintenance phase)	Triangular	$0.11 (min: 0.11, likeliest: 0.11, max: 0.12)
LTBI & Active TB	Cost of daily DS-TB meds: RHZE (intensive phase)	Triangular	$0.24 (min: 0.23, likeliest: 0.24, max: 0.24)
LTBI & Active TB	Cost of Drug susceptibility testing (1 sample)	Triangular	$23.11 (min: 9.91, likeliest: 19.81, max: 39.62)
LTBI & Active TB	Cost of TB pre-diagnosis consultation: initial assessment	Triangular	$17.42 (min: 7.47, likeliest: 14.93, max: 29.87)
LTBI & Active TB	Cost per Culture	Triangular	$9.76 (min: 4.18, likeliest: 8.37, max: 16.73)
LTBI & Active TB	Cost per CXR	Triangular	$16.48 (min: 7.06, likeliest: 14.13, max: 28.26)
LTBI & Active TB	Cost per Follow-up visit with medical doctor	Triangular	$17.34 (min: 7.43, likeliest: 14.86, max: 29.73)
LTBI & Active TB	Cost per Liver Function Test	Triangular	$4.39 (min: 1.88, likeliest: 3.79, max: 7.5)
LTBI & Active TB	Cost per sputum smear (per sample)	Triangular	$3.42 (min: 0.89, likeliest: 3.13, max: 6.25)
LTBI & Active TB	Cost per Xpert MTB/RIF	Triangular	$17.42 (min: 7.47, likeliest: 14.93, max: 29.87)
LTBI & Active TB	Cost of TB pre-diagnosis complementary exams	Gamma	$3.46
LTBI	Cost: AE-related additional lab tests	Triangular	$17.64 (min: 7.56, likeliest: 15.12, max: 30.24)
LTBI	Cost: consult with specialist (2) (nurse + MD)	Triangular	$11.07 (min: 4.75, likeliest: 9.49, max: 18.98)
LTBI	Cost: medical visit or LTBI standard FU visit (nurse + MD)	Triangular	$5.54 (min: 2.37, likeliest: 4.75, max: 9.49)
LTBI	Cost of pre-diagnosis consultation: initial assessment	Triangular	$17.42 (min: 7.47, likeliest: 14.93, max: 29.87)
LTBI	Cost of pre-diagnosis complementary exams	Gamma	$3.46
	Patient costs		
LTBI & Active TB	Patient declared income per hour	Triangular	$2.20 (min: 1.5, likeliest: 1.9, max: 3.2)
LTBI & Active TB	Patient training duration (in min)	Triangular	7.5 (min: 5, likeliest: 7.5, max: 10)
LTBI & Active TB	Patient cost for 6 months (excluding hospitalization)	Gamma	$257.18
LTBI & Active TB	Patient direct hospitalization cost	Gamma	$7.22
LTBI & Active TB	Patient indirect hospitalization cost	Gamma	$34.47
LTBI & Active TB	Total patient cost excluding hospitalization – 6-months treatment	Gamma	$98.33
LTBI & Active TB	Total patient direct & indirect costs Before TB diagnosis	Gamma	$83.01
	DALYs		
LTBI & Active TB	DALY weight for active TB (Treated TBD)	Triangular	0.17 (min: 0.11, likeliest: 0.17, max: 0.23)
LTBI & Active TB	DALY weight for active TB (Untreated TBD)	Triangular	0.34 (min: 0.22, likeliest: 0.33, max: 0.45)
	Probabilities		
LTBI & Active TB	Probability of cure & complete DS-TB treatment	Beta	73%
LTBI & Active TB	Probability of default during MDR-TB treatment	Beta	17%
LTBI & Active TB	Probability of failed DS-TB retreatment	Beta	3%
LTBI & Active TB	Probability of LTFU/Transfer during TB treatment	Beta	19%
LTBI & Active TB	Probability of LTFU/Transfer TB retreatment	Beta	39%
LTBI & Active TB	Probability of TB treatment failure	Beta	1%
LTBI & Active TB	Probability of TB-related death during DS-TB treatment	Beta	8%
LTBI & Active TB	Probability of TB-related death during MDR-TB treatment	Beta	10%
LTBI & Active TB	Probability of TB-related death during retreatment	Beta	8%
LTBI & Active TB	Probability of treatment failure when immediately retreated following a failed DS-TB treatment	Beta	6%
LTBI & Active TB	Probability of retreatment after TB relapse	Triangular	87% (min: 75%, likeliest: 87%, max: 100%)
Active TB	Probability of MDR-TB related death during retreatment	Beta	16%
Active TB	Probability of failed TBD retreatment	Beta	25%
Active TB	Probability of LTFU/Transfer MDR-TB retreat	Beta	34%
Active TB	Probability of having non-severe adverse event from TB treatment	Beta	10%
Active TB	Probability of having severe adverse event from TB treatment	Beta	2%
LTBI	Probability of progression of LTBI to TB disease	Triangular	7% (min: 2%, likeliest: 5%, max: 15%)
LTBI	Probability of LTBI reactivation to TB disease	Triangular	0.13% (min: 0.1%, likeliest: 0.1%, max: 0.2%)
LTBI	Probability of diagnosis of TB disease after LTBI progression	Triangular	87% (min: 75%, likeliest: 87%, max: 100%)
LTBI	Probability of LTBI cure after full course of treatment	Triangular	90% (min: 80%, likeliest: 90%, max: 100%)
LTBI	Probability of relapse to TB disease after cured TB disease in	Triangular	2% (min: 0.75%, likeliest: 1.5%, max: 2.5%)

3. RESULTS: Sensitivity analyses

Active TB cohorts

Using MM, the two main determinants of overall cost were that of the medication dispenser and that of the standard follow-up visit. Using the VOT intervention, the cost of the standard follow-up visit was projected to be most influential cost parameter (Figure S3).

LTBI cohort

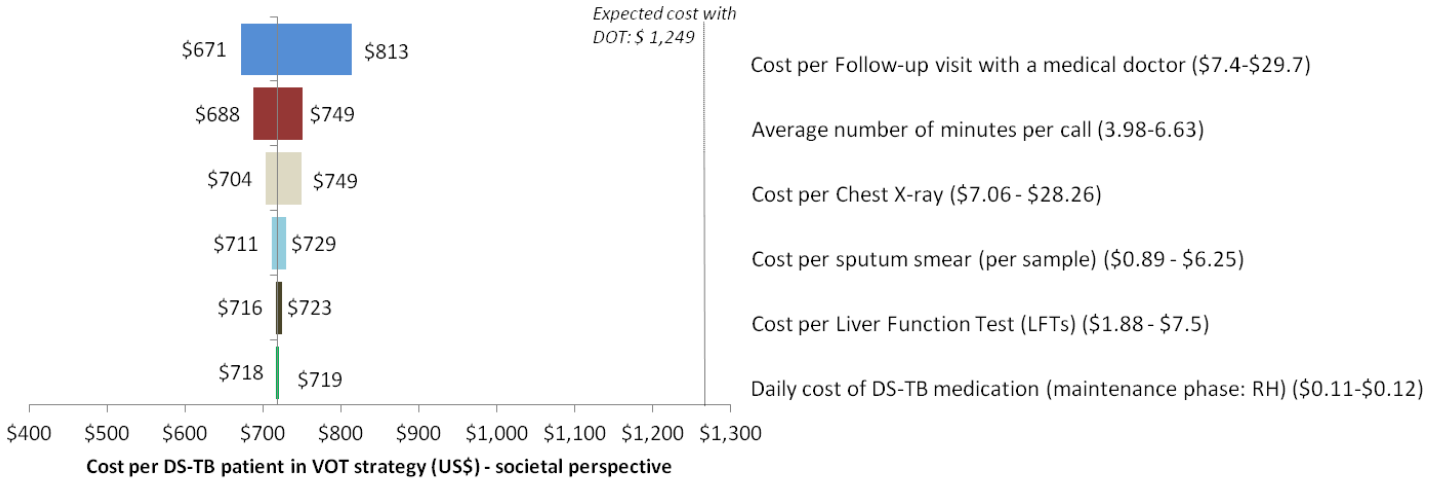
In univariate sensitivity analyses focusing on cost per TB case prevented, the probability of progressing from LTBI to active TB was the most influential model parameter for all digital strategies (Figure S4). Univariate sensitivity analyses focusing on cost per DALY averted indicated that the probability of progressing from LTBI to active TB and the effectiveness of the digital health intervention (relative probability of treatment completion) were highly influential for all digital strategies (Figure S5).

Threshold analyses demonstrated that for all technologies, only a minimal increase in efficacy relative to SAT was required for the interventions to be considered relatively cost-effective (incremental cost per DALY averted less than the Brazilian per capita GDP). The relative risk/probability (RR) for treatment completion above which each intervention was considered relatively cost-effective were 1.001 for SMS and 99DOTS®, 1.007 for Wisepill®, and 1.06 for VOT.

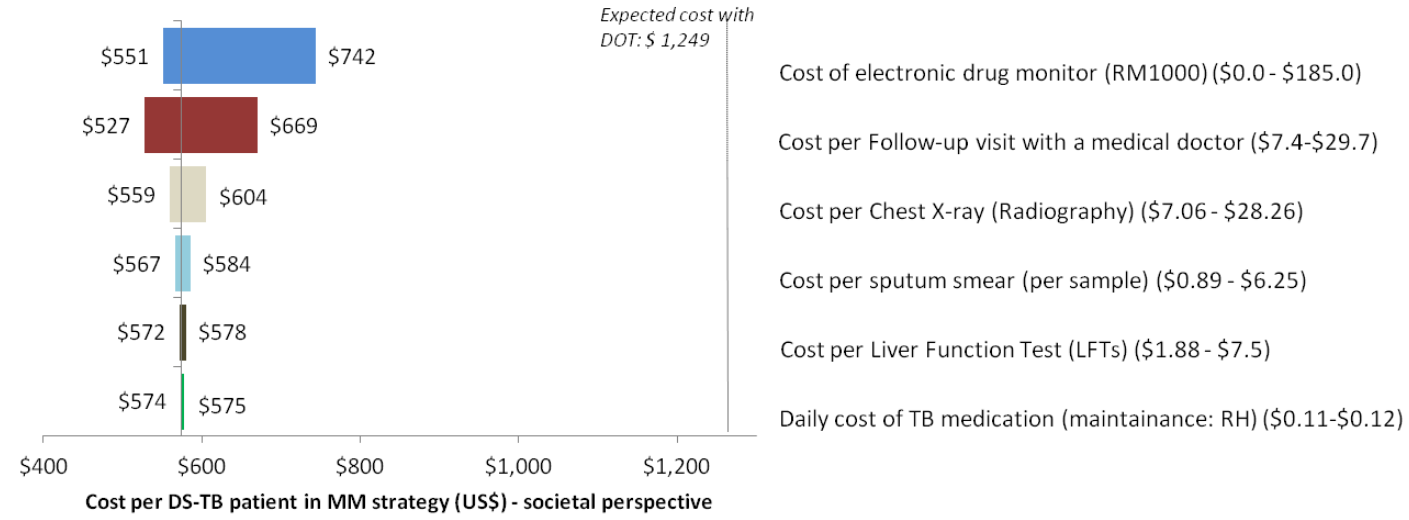
Cost-effectiveness acceptability curves, which represent the probability that the implementation of each digital intervention will be cost-effective relative to SAT as a function of the decision-makers' willingness-to-pay, are shown in Figure S6.

Figure S3: Tornado diagrams of the results of univariate sensitivity analyses with respect to the total costs related to the treatment of active TB using (i) video-observed therapy for DS-TB; (ii) Wisepill medication monitors for DS-TB; (iii) 99DOTS medication monitors for DS-TB; (iv) video-observed therapy for MDR-TB; (v) Wisepill medication monitors for MDR-TB; (vi) 99DOTS medication monitors for MDR-TB

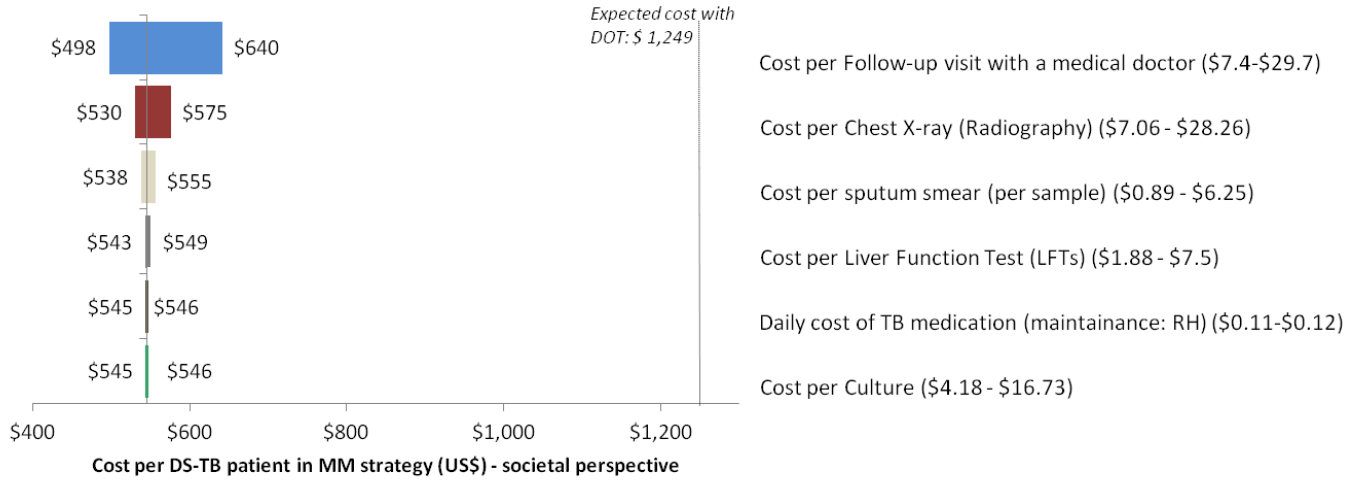
(i) VOT strategy for DS-TB



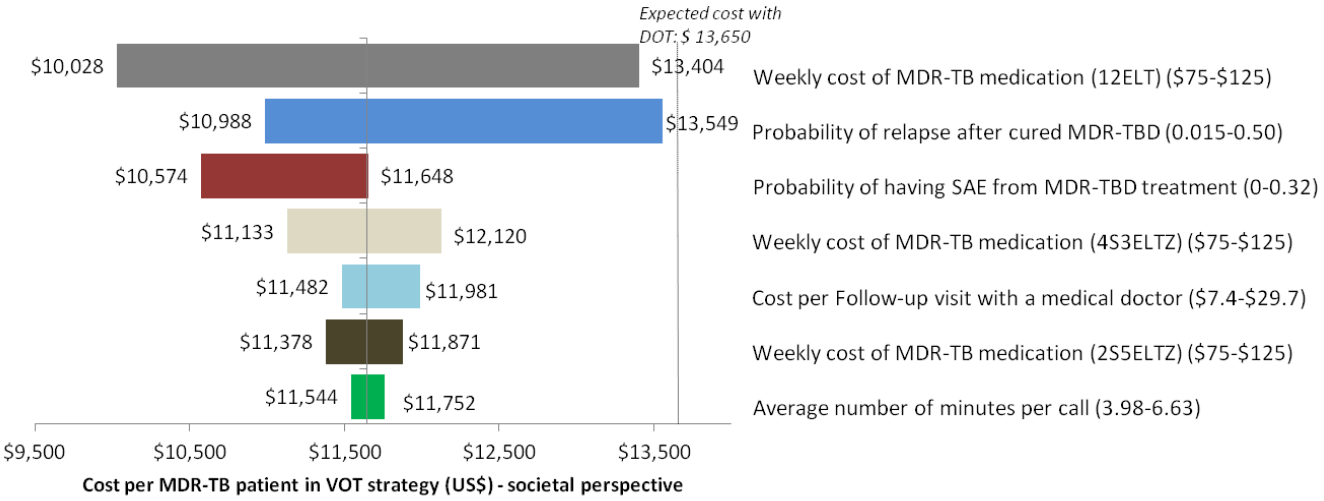
(ii) Wisepill medication monitor strategy for DS-TB



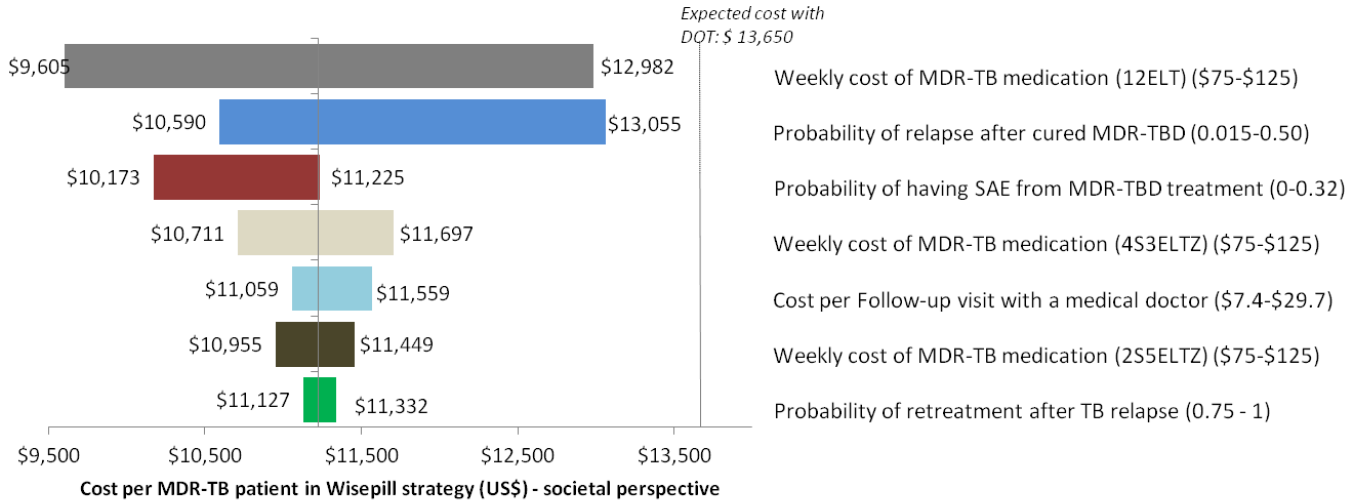
(iii) 99DOTS medication monitor strategy for DS-TB



(iv) VOT strategy for MDR-TB



(v) Wisepill medication monitor strategy for MDR-TB



(vi) 99DOTS medication monitor strategy for MDR-TB

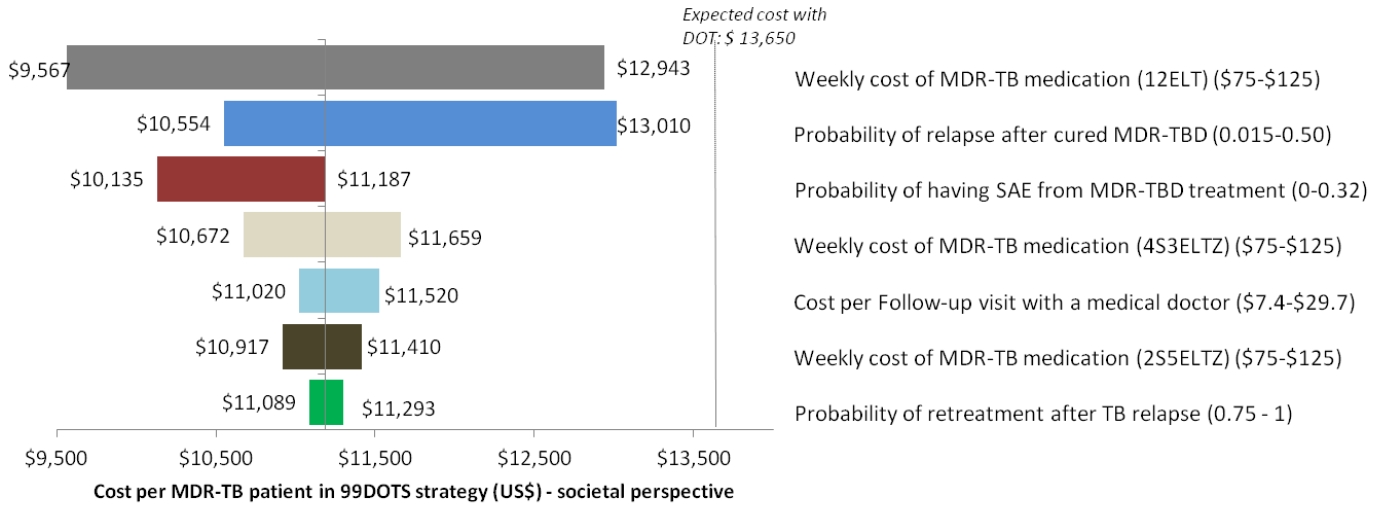
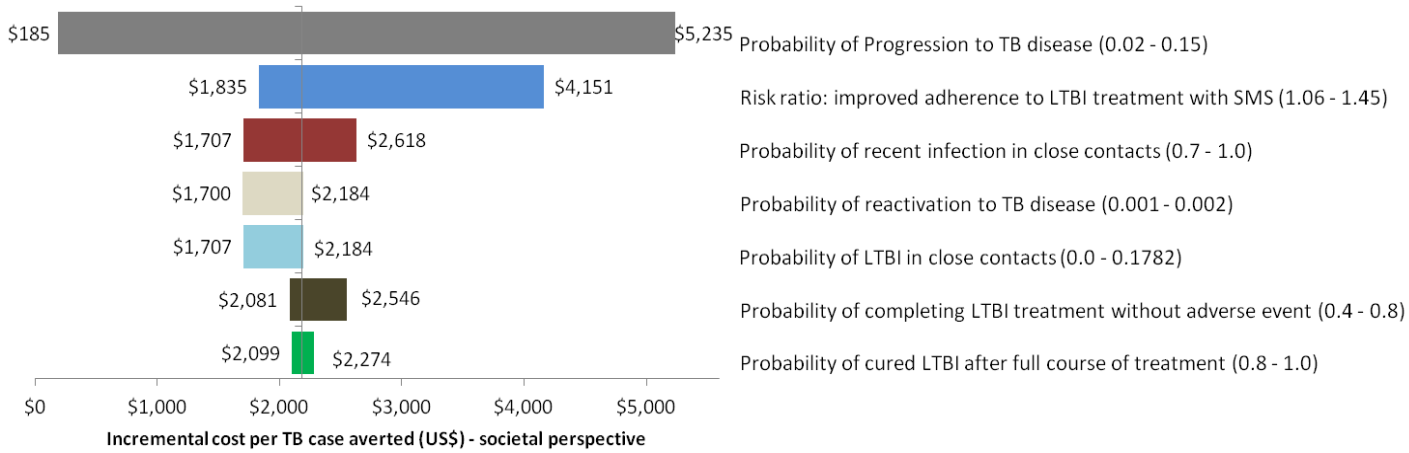
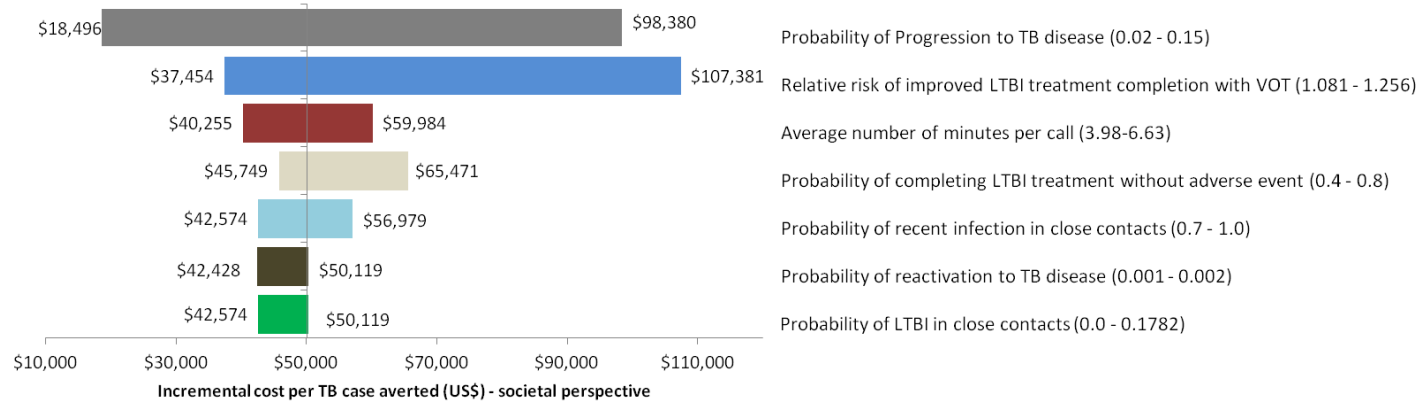


Figure S4: Tornado diagrams of the results of univariate sensitivity analyses with respect to TB cases averted, in the treatment of latent TB infection using (i) two-way SMS; (ii) video-observed therapy; (iii) Wisepill medication monitors; and (iv) 99DOTS medication monitors

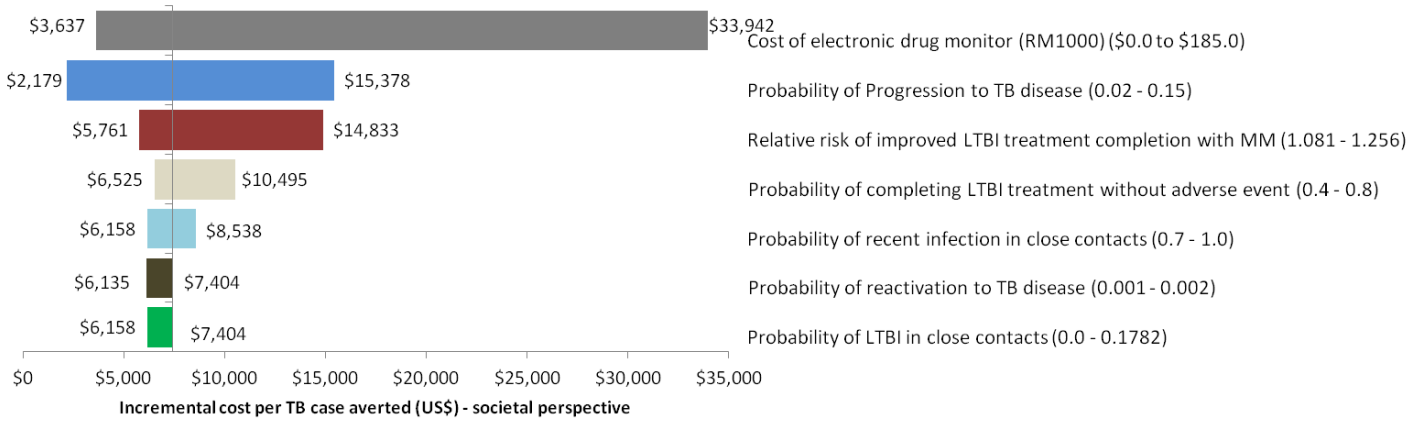
(i) SMS strategy



(ii) VOT strategy



(iii) Wisepill medication monitor strategy



(iv) 99DOTS medication monitor strategy

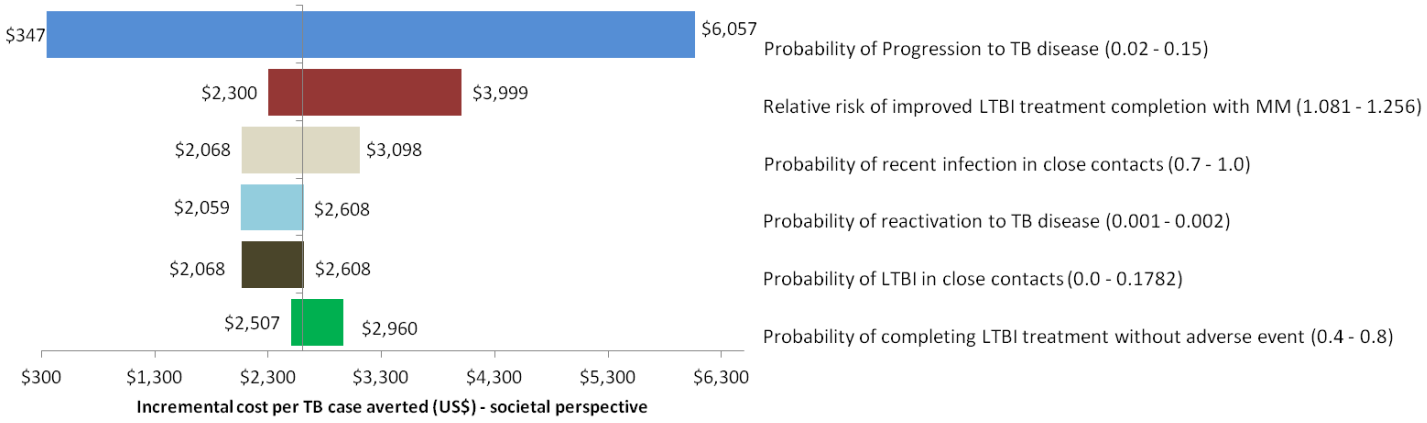
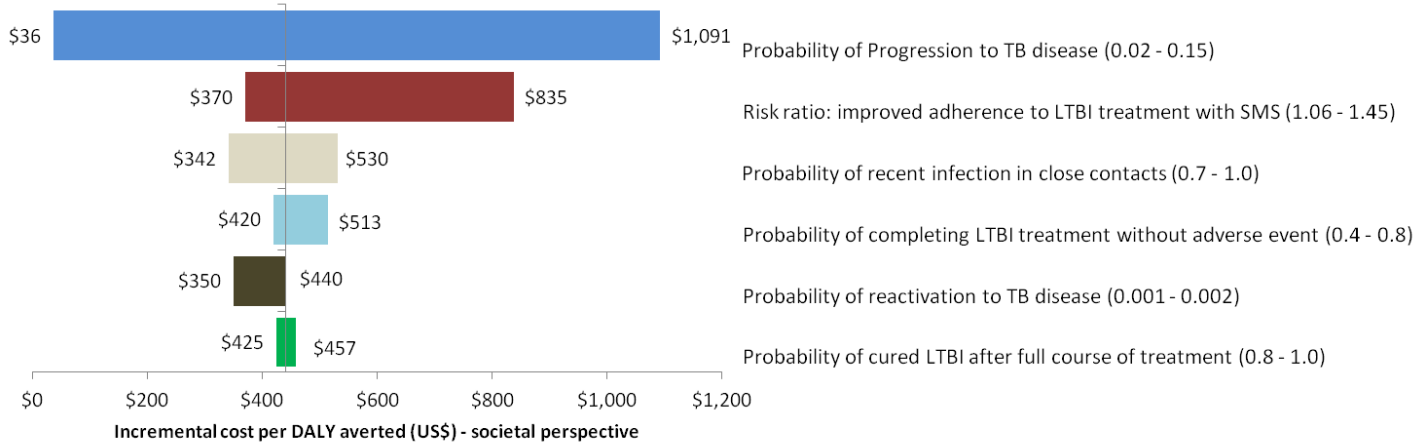
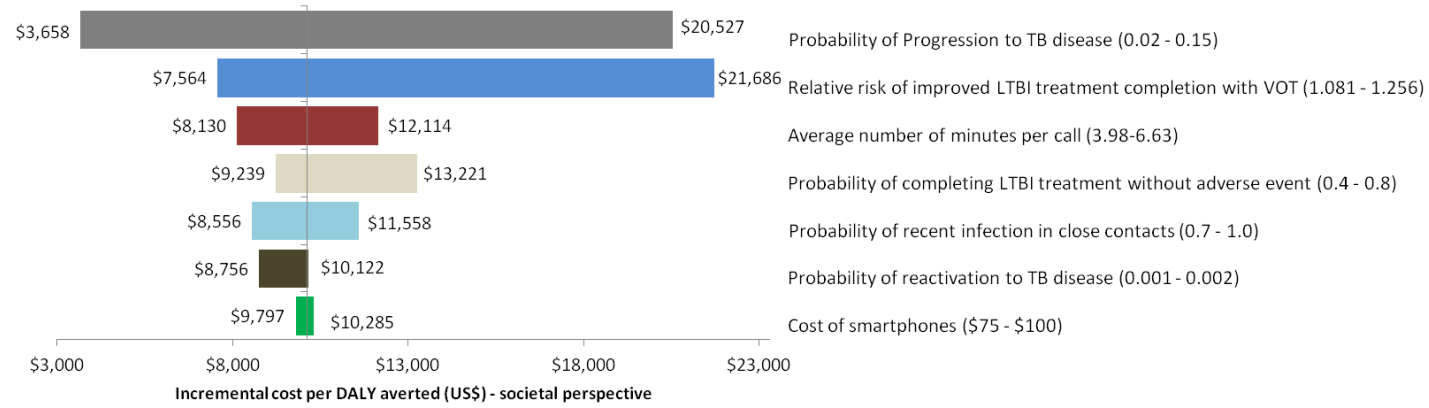


Figure S5: Tornado diagrams of the results of univariate sensitivity analyses with respect to DALYs averted, in the treatment of latent TB infection using (i) two-way SMS; (ii) video-observed therapy; (iii) Wisepill medication monitors; and (iv) 99DOTS medication monitors

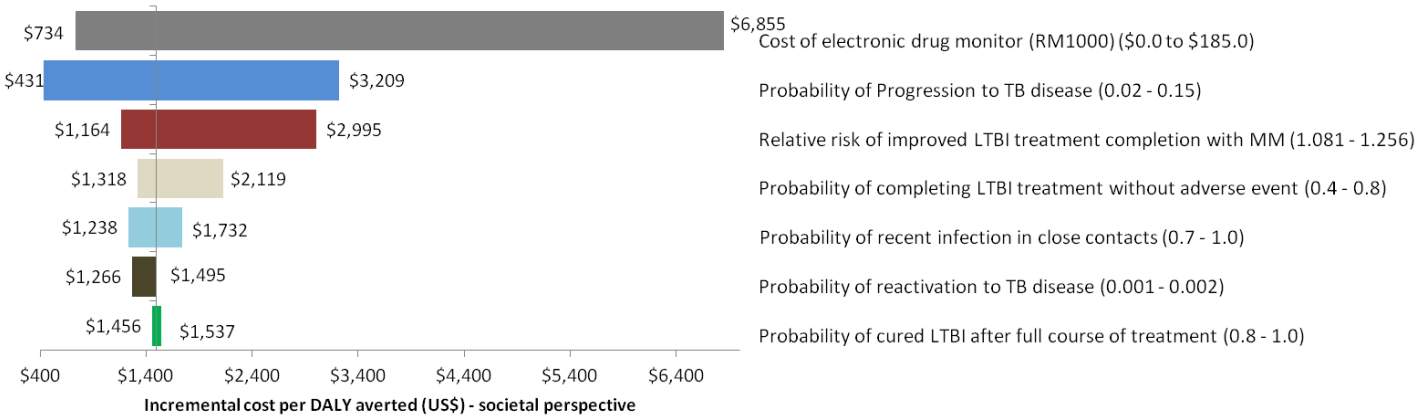
(i) SMS strategy



(ii) VOT strategy



(iii) Wisepill medication monitor strategy



(iv) 99DOTS medication monitor strategy

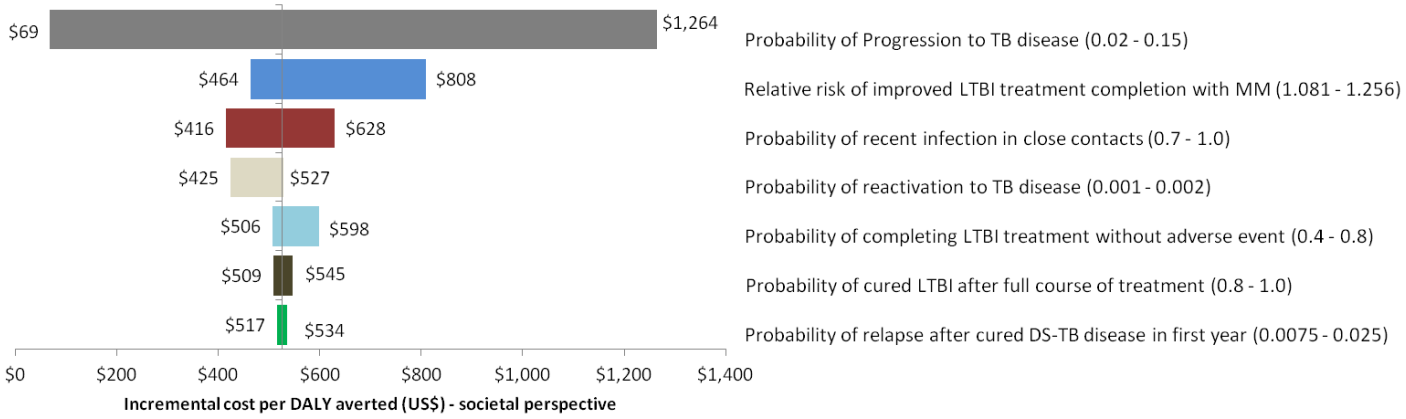
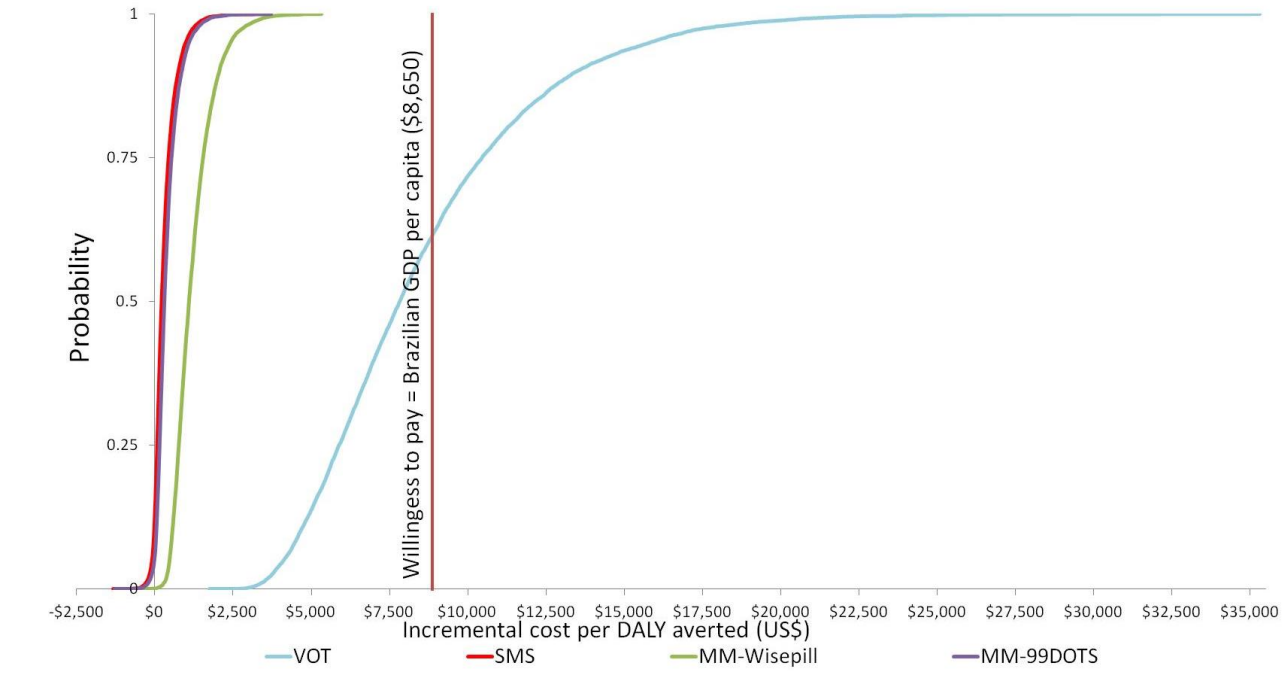
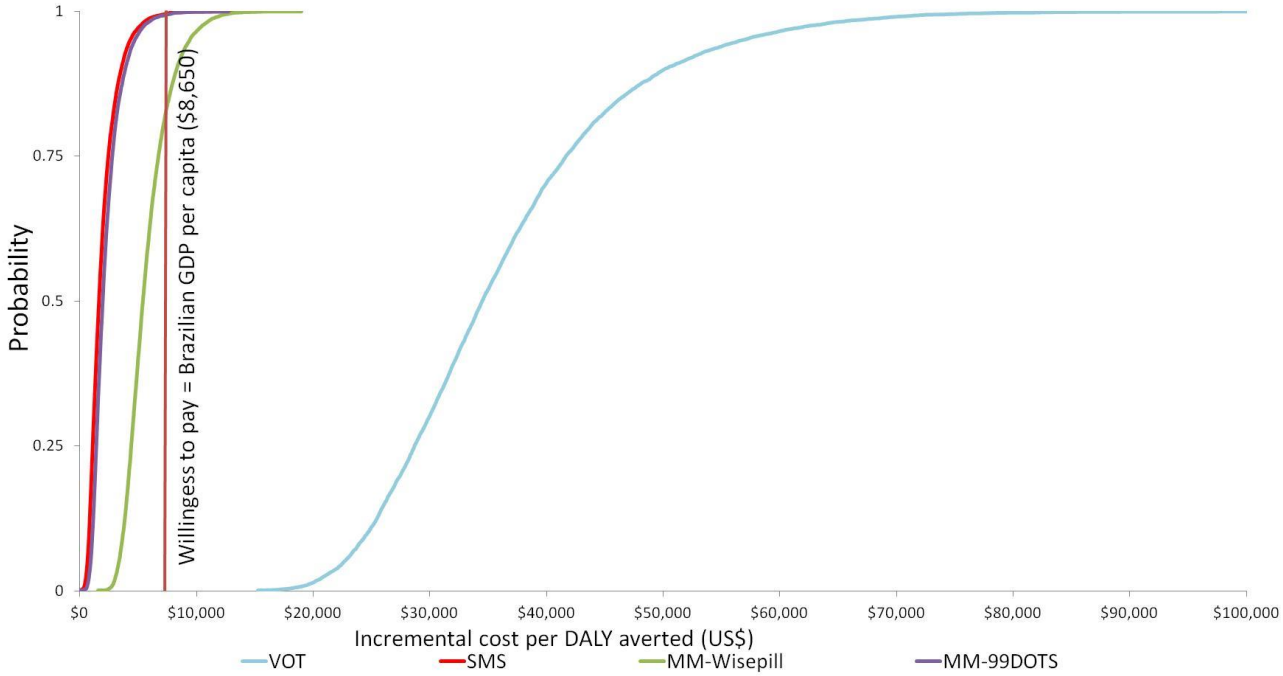


Figure S6. Cost-effectiveness acceptability curves comparing digital interventions to self-administered treatment, among (i) close contacts of persons with active TB having tested positive for LTBI and (ii) members of the general population having tested positive for LTBI



(i)



(ii)

SMS, short message service. VOT, video-observed therapy. MM, medication monitor. WTP, willingness-to-pay. GDP, gross domestic product ($US8,539) [70]. Curves show the probability that the digital intervention is cost effective vs. self-administered treatment as a function of the decision-marker's WTP. For reference, the 2016 Brazilian gross domestic product per capita plotted as an estimate of the Brazilian TB program's WTP [70].

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