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Early View

Perspective

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

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

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ABSTRACT

Ensuring adherence and support during treatment of tuberculosis (TB) is a major public health challenge. Digital health technologies could help improve treatment outcomes. We considered their potential cost and impact on treatment for active or latent TB in Brazil.

Decision analysis models simulated two adult cohorts with 1) drug-susceptible active TB, and 2) multidrug-resistant TB; and two cohorts treated with isoniazid for latent TB infection (LTBI): 1) close contacts of persons with active TB, and 2) others newly diagnosed with LTBI. We evaluated four digital support strategies: two different medication monitors (MMs), synchronous video-observed therapy (VOT), and two-way short message service (SMS). Comparators were standard directly observed treatment for active TB and self-administered treatment for LTBI. Projected outcomes included costs (2016 USD), plus active TB cases and disability-adjusted life years (DALYs) averted among persons with LTBI.

For individuals with active TB, MMs and VOT are projected to lead to substantial (up to 58%) cost savings, in addition to alleviating inconvenience and cost to patients of supervised treatment visits. For LTBI treatment, SMS and MMs are projected to be the most cost-effective interventions. However, all projections are limited by the scarcity of published estimates of clinical effect for the digital technologies.

INTRODUCTION

Tuberculosis burden and treatment challenges

Approximately one quarter of the world's population is estimated to be infected with latent tuberculosis (LTBI) [1, 2], and each year, about 10 million individuals develop active tuberculosis (TB) [3, 4]. Despite the success of some strategies to reduce the global TB burden [5], TB remains a leading cause of mortality worldwide, causing an estimated 1.7 million deaths in 2016. Implementation challenges impede the success of directly observed treatment (DOT), as TB treatment is labor intensive for both patients and health care providers, requiring rigorous commitment from all to achieve good adherence and treatment success [6]. An effective DOT program allows early detection and mitigation of suboptimal adherence, which otherwise leads to poorer patient outcomes, including acquired drug resistance [7], and increased costs for both the health system and patient. The latest global treatment success rates reported in 2016 were 83% among new and relapse TB patients, and 54% among persons with multidrug-resistant TB (MDR-TB, resistance to rifampicin and isoniazid) [8].

The World Health Organization's (WHO) End TB Strategy aims to halt the TB epidemic by 2035. Beyond better adherence to treatment for active TB, this strategy also calls for improved detection and management of LTBI in countries with high and low TB burdens [9-11]. Obstacles to the uptake and completion of LTBI therapy include the need for testing and medical evaluation, treatment length and risks, and the necessity of follow-up visits with care providers [12, 13]. LTBI treatment is generally self-administered without supervision; consequently, adherence is inconsistent. A meta-analysis published in 2016 estimated that only 62% of persons starting preventive therapy completed treatment [12]. Only 13% of eligible contacts under 5 years and 42% of people newly enrolled in HIV care were estimated to have started preventive treatment for latent TB infection in 2016, well below the target of 90% or more envisaged for these subpopulations by the End TB Strategy for 2025 [8, 14]. Measures to improve treatment coverage and completion could increase the contribution of preventive therapy to reduce global TB incidence in the coming years.

Adherence support

Digital technologies have been evaluated extensively and used successfully to improve outcomes in HIV and other chronic diseases. They have been associated with improved adherence to treatment, with some initial evidence in the TB context [15-18]. The WHO guidelines on the management of latent tuberculosis infection (LTBI) recommend monitoring

treatment using digital technologies [19] to further patient-centred care and support, key elements of the TB elimination framework [20]. Indeed, in 2016, WHO's Global Consultation on the Programmatic Management of LTBI called for digital technologies to be used in managing and treating LTBI [21], and in 2017 the Global TB Programme of the WHO released its first evidence-based recommendations on the use of digital technologies in support of TB treatment administration and adherence [22]. These guidelines acknowledged that further evidence is needed to understand the feasibility of implementing digital health technologies, and to measure the impact they could have on TB prevention and care [23-25]. In particular, evidence of the clinical impact of these interventions remains limited to date [18].

Published evaluations of digital health interventions in active TB and LTBI care have provided limited information about cost [26, 27]. Each digital health technology may entail substantial investment in hardware, software, and/or infrastructure. Given the scarce funds for TB prevention and care, such costs must be considered alongside any anticipated gains in health outcomes. In this article, we use decision analysis models to begin to explore the costs and potential clinical impacts of the widely available and scalable technologies that are currently best positioned to replace in-person treatment observation for either active TB, and/or to support treatment for LTBI which is currently self-administered. The technologies considered include video-observed therapy (VOT), electronic medication monitors (MM), and two-way text messaging (SMS). We consider their use in Brazil, a high TB-burden setting with widespread access to smartphones and telephone network/internet coverage.

METHODS

General Description of Models

For active TB disease, a decision analysis model was developed to simulate cohorts of 35 year-old adults (both sexes) who initiate TB treatment in Brazil. Patients were assumed to have either DS-TB (model 1) or MDR-TB (model 2). The simulation began at treatment initiation and allowed for two rounds of treatment if needed, representing a time horizon of two to four years. Two digital health interventions, VOT and MM, were compared against standard DOT for treatment support of DS-TB and MDR-TB. We did not consider SMS support of active TB treatment, for reasons detailed below.

For LTBI, a decision analysis model simulated two cohorts of 35 year-old adults (both sexes) diagnosed with LTBI in Brazil. One cohort was comprised of individuals diagnosed with LTBI

who were close contacts of drug sensitive active TB cases. The other cohort consisted of members of the general population diagnosed with LTBI. Simulations began at treatment initiation and lasted 20 years. Nine months of daily isoniazid, supported by SMS, VOT, or MM, were compared with self-administered treatment, the standard of care for LTBI.

In all models, outcomes included disability-adjusted life years (DALYs) and costs for each strategy. For the LTBI cohorts, future incident TB cases were also projected.

Costs were expressed in 2016 US dollars (USD) and were projected from both the health system and societal perspectives. Where appropriate, cost-effectiveness was evaluated using incremental cost-effectiveness ratios (ICERs). Models were developed using TreeAge Pro 2016 software (TreeAge Software Inc. Williamstown, MA). Simplified schemas of the decision analysis models are included in the appendix.

Study Setting

Brazil is a high TB-burden country: in 2016 it had an estimated incidence of 87,000 TB cases (95% CI 74,000 to 100,000) at a rate of 42 cases per 100,000 population [8]. It has a comprehensive disease database, SINAN, [SINAN 2010-2016] (http://portalsinan.saude.gov.br/ Date last accessed: July 29, 2016), providing up-to-date clinical and TB programme data. This setting was chosen in part because of Brazil's high mobile-broadband penetration; in 2015 it had an 88% penetration, and was ranked 4th globally in active internet users [28].

Digital Interventions

Digital health interventions were selected on the basis of a recent systematic review of digital technologies for TB [18]. Below is a summary of the strategies included.

Medication Monitors

Two MM strategies were considered for treatment support for both active and latent TB: Wisepill® and 99DOTS. A randomized trial of treatment support for active TB in China reported that patients using MM had 0.58 (95% CI: 0.42-0.79) times the number of patient-months with 20% or more missed doses as those on standard care [29]. However, an impact on clinical outcomes was not demonstrated. In the primary analysis, we therefore made the conservative assumption that for active TB, MM would yield treatment outcomes comparable to standard care with direct observation. There are no randomized studies evaluating MM in LTBI care. Thus, in

the LTBI model, we assumed that MM would lead to better adherence than SAT in a context where support for LTBI treatment is very limited; we derived estimates of effect from the same trial in China [29]. A relative risk (RR) of 1.18 (95% CI: 1.08 - 1.26) for treatment completion was calculated using published data from the Chinese trial (see appendix for detailed calculations).

VOT

VOT was considered for treatment support for both active and latent TB. The VOT intervention was adapted from an observational study of active TB treatment support in New York City in 2014 [30]. The New York City study reported adherence with VOT of 95% of doses, compared to 91% for in-person DOT ($p < 0.01$). In our active TB model, we thus assumed that treatment success rates using VOT for active TB were equivalent to those for in-person DOT. There are no published trials or other studies of VOT performed to monitor LTBI treatment. We assumed that VOT was likely to improve adherence to LTBI treatment relative to SAT. Thus, we assumed that the effect of VOT for LTBI would be equivalent to that of MM.

SMS

Because randomized studies have suggested SMS is not well-suited to active TB care, we did not model this intervention in the context of active TB [31]. The two-way SMS intervention for LTBI was adapted from a study from British Columbia, Canada [32]. LTBI is usually treated using SAT, as is the case for HIV. We relied on the largest published randomized trial of two-way SMS for HIV treatment in Kenya (538 participants) [33], and assumed that the effect of two-way SMS on treatment completion was similar for LTBI and HIV. Again, extrapolating from the Kenyan trial, we assumed that SMS was likely to improve treatment support and completion in a context where existing support for LTBI treatment is very limited.

Table 1 provides more operational details and summarizes the effect estimates for all digital interventions considered.

Table 1: Details of digital support interventions for treatment of active TB and LTBI

Digital technologies[#]	Operational details	Estimate of effect	
		Active TB	**LTBI**
MM: Wisepill®	• Small device attached to standard pill dispenser • When opened, device communicates with web-based application by SMS • Device sends SMS to patient and HCW when daily dose is missed. • One-way texting: no response is required of patient. [34-36]	Assumed effect was equivalent to DOT/standard of care.	Assumed effect was equivalent to that of MM in trials of active TB: patients using digital interventions were 1.18 (95% CI 1.08-1.26) times more likely to complete treatment than those on SAT. (Derived from [29])
MM: 99DOTS®	• Taking pills from blister pack daily reveals random toll-free numbers • Any call from a registered patient number is marked as a dose taken • When patients call, they hear 'thank you'. • Automatic alerts to patients and HCW of missed doses • Open source IT system [37, 38]		
VOT	• Smartphone loaned to patients without one • Pre-arranged schedule for real-time (synchronous) daily VOT calls with HCW • Patient shows and names pills, then swallows them. • Patient asked about adverse reactions. • Missed appointments followed up first by phone calls, then by home visits [30]		
Two-way SMS *(LTBI model only)*	• Weekly SMS 'check-ins' sent from central computer at clinic • Patients asked to respond within 24 hours • First instance of non-response: follow-up SMS • Second instance of non-response: phone call [32]	N/A	Assumed effect was equivalent to that of two-way SMS in trials of HIV: patients using digital intervention were 1.24 (95% CI: 1.06-1.45) times more likely to complete treatment than those on SAT[33]

[#] Routine in-person DOT visits were replaced by digital technologies for active TB treatment supervision.
SMS, short message service. VOT, video-observed therapy. MM, medical monitor. SAT, self-administered treatment. HCW, healthcare worker.

Data sources

Pathogenesis, natural history of TB, epidemiology and drug resistance data were taken from published literature, and are summarized in Table A3 in the appendix. Treatment outcomes were derived from 2013-2014 country-specific data from the Brazilian National TB Program (Table A1, appendix). For cost-utility analyses, a weight of 0.331 DALYs was attributed to active

TB (95% CI: 0.224-0.454) [39], and a weight of 0 DALYs was attributed to LTBI, as individuals with LTBI are asymptomatic (Table A3, appendix). Further description of the DALY calculations is provided in the appendix.

Costs

All costs were expressed in 2016 US dollars, using relevant exchange rates and published inflation indices for Brazil and for any other countries from which cost data were obtained (see appendix). Costs obtained from India and South Africa were normalized to the Brazilian per capita gross national income (GNI), by multiplying them by (Brazilian per capita GNI ÷ Indian/South African per capita GNI for the relevant year). During the 20-year simulation of individuals with LTBI, all future costs and outcomes were discounted at an annual rate of 3%.

Digital technology costs

Technology costs included materials required to implement the interventions such as phones, dispensers and envelopes. Start-up and follow-on operational costs for each technology, training costs and staff pay based on the time needed to complete an activity, including steps taken to follow up with patients reporting problems or demonstrating suboptimal adherence, were also incorporated. Table 2 serves as an example of the types of cost components included for the SMS intervention and is shown as a per person cost. Detail cost breakdowns for all other interventions are shown in the appendix Table A9.

Table 2: Digital technology costs for treatment support using two-way text messaging (SMS), per person with LTBI [υ]

		Value	Reference
Text Messaging (SMS)			
a)	Server: Cost of one Server (3 servers needed, 1 server/100,000 patients)	$2,000	#
b)	Server: start-up cost (per patient) [ɦ]	$0.02	Calculated from a)
c)	Server: monthly server fees (unit cost)	$960	#
d)	Server: monthly fee (per patient)	$0.01	Calculated from c)
e)	Data & Phone costs per patient per month	$0.21	##
f)	Number of messages per month (1/week)	4.3	
g)	Cost of a single SMS, Brazil	$0.02	www.mobilepronto.com
h)	Proportion of patients who respond to SMS with a problem	0.06	*
i)	Proportion of patients who do not respond to first SMS	0.38	[12]**
j)	HCW time required to respond to patient who does not respond (min) – 2nd SMS	1.5	Hwang mHealth poster
k)	HCW time requires to respond to patient with problem (min)	20	Assumption ###
l)	Mean, weighted HCW time/patient (min) (h*k + i*j)	1.81	Calculated
m)	TB nurse wage/minute	$0.16	
n)	*Subtotal – treatment support cost (l*m)*	*$0.29*	

		Value	Reference
o)	*Mean, weighted message/phone costs associated with 2nd SMS for patients who do not respond (to be added to all patients) (g*i)*	*$0.01*	
p)	*Mean nurse training cost (pro-rated per LTBI case)*	*$3.35*	[#] calculated
Complete cost for 9-months LTBI treatment support [b + 9*(d + e +f*g) + n + o + p] per person		**$6.32**	

[υ] The aggregate cost does not include cost components related to diagnosis or treatment (see table 3)
[#] Personal communication with WelTel's Dr. Richard Lester [33]
[###] Clinic cost/mean number of patients per clinic (WelTel)/36 months (length of WelTel Trial) [33, 40]
[####] Time on the phone is assumed equivalent in minutes to in-person adverse event consultation (20 min)
[ħ] 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))
[*] Assumption: equivalent to total AE rates for LTBI
[**] Assumption: Complement of the reported global LTBI treatment completion rate, conditional on initiating treatment

Treatment-related health system costs

Health system costs included staff salaries for all DOT and other follow-up visits, costs of follow-up monitoring tests, and drug costs. DOT visits were assumed to occur three times weekly, as recommended by Brazilian authorities [41], with other treatment doses self-administered. For re-treatment, diagnostic costs were also included. Hospitalization and adverse event management costs were based on published estimates [42, 43] (Tables A4-A7, appendix). Patient costs were classified as direct (out-of-pocket expenses related to medical visits) and indirect (time lost due to medical visits) (Table A8, appendix). Table 3 summarizes aggregate cost inputs used for standard treatment regimens for the different cohorts, and for each of the intervention scenarios. These aggregate costs reflect the costs incurred by the health system and patient for diagnosis and treatment (varying depending on type of TB), plus any additional costs relevant to each of the specific digital technologies (as shown for SMS in Table 2).

Table 3: Total input cost per person with TB or LTBI for diagnosis and treatment (health system and patient perspective), by type of digital technology used for treatment support, in 2016 USD

	Total costs related to diagnosis and treatment-incurred by health system					**Total cost related to diagnosis and treatment incurred by patient**	
	Standard of care	**VOT**	**MM: Wisepill®**	**MM: 99DOTS®**	**SMS**	**Standard of care**	**Digital tech.**
Drug-susceptible: 6-months treatment	$845	$505	$368	$340	N/A	$299	$140
MDR-TB: 18-months treatment	$10 014	$8 879	$8 527	$8 494	N/A	$813	$337
LTBI: 9 months treatment	$53	$397	$91	$61	$59	$148	$148

SMS, short-message service. VOT, video-observed therapy. MM, medication monitors. N/A, not applicable.
Costs listed account for pre-diagnostic management, diagnosis, treatment, and follow-up.

Scenario and sensitivity analyses

Due to the paucity of empiric data on clinical outcomes with the digital interventions, we considered several alternative scenarios to those described above. For active TB, we considered the possibility that MM and VOT may actually improve TB treatment outcomes relative to DOT. In this scenario, we assumed that improved adherence as reported in China would lead to improved treatment success rates, and applied the ratio reported by Liu et al to unfavorable treatment outcomes (LTFU, death and failure) in the MM and VOT intervention arms of the model.

An alternative analysis for the LTBI cohorts focused only on cost differences between scenarios, setting the effect of all interventions to be equivalent to that used for MM in the baseline analyses (i.e. RR=1.18 for treatment completion, compared to SAT). Additionally, a threshold analysis was conducted for the LTBI cohort to identify the minimal efficacy required of the intervention in order for it to remain cost effective when considering DALYs averted.

Probabilistic sensitivity analyses (PSA) were used to generate 95% Uncertainty Ranges (UR; 2.5^{th} and 97.5^{th} percentiles) around point estimates for all projected outcomes. They were also used to further explore the potential cost-effectiveness of these technologies. Additional sensitivity analyses, including one-way sensitivity analyses for key parameters used in each model and relevant tornado diagrams, are described in the appendix.

RESULTS

Health system perspective

Drug-susceptible-TB and MDR-TB cohorts

Assuming equivalent DS-TB treatment success rates with DOT and digital interventions, all interventions led to health systems cost savings relative to standard DOT, ranging from 39% to 58%. For the MDR-TB cohort, all digital interventions also led to health system cost savings, where treatment success rates were assumed to be equivalent to those with DOT. Relative to DOT, cost savings ranged from 11% to 15%. Further details are provided in Table 4.

LTBI cohort

Among close contacts with LTBI, SMS and the MMs were projected to be most cost-effective compared to SAT. The incremental cost of SMS was $5 per person, with a reduction in DALYs of 0.04 per person, and a 0.8% absolute decrease in future TB incidence over the 20-year simulation. The incremental cost of SMS was $123 per DALY averted, and $611 per TB case prevented. Both MMs and VOT averted 0.03 DALYs per person, and led to an absolute reduction in TB incidence of 0.6%. The 99DOTS® MM was the second most cost-effective intervention, with an incremental cost of $210 per DALY averted, and $1,038 per TB case prevented. The Wisepill® MM had an incremental cost of $1,178 per DALY averted, and $5,836 per TB case prevented. VOT had an incremental cost of $9,805 per DALY averted, and $48,551 per TB case prevented. Complete results are shown in Table 5.

Among persons from the general population with LTBI, SMS was the most cost-effective intervention. SMS cost $1,000 per DALY averted and $4,483 per TB case prevented compared to SAT (Table 5).

Societal perspective

Drug-susceptible-TB and MDR-TB cohort

Combining health system and patient costs, cost savings with digital technologies for the DS-TB cohort ranged from 43% to 56%, and from 15% to 18% for MDR-TB, relative to standard DOT.

Estimated savings to patients were $168 for each DS-TB patient and $593 for each MDR patient. See table 4 for full details.

LTBI cohorts

In both LTBI cohorts, results from the societal perspective (Table 5) were similar to those from the health system perspective. In close contacts, SMS was projected to be the most cost-effective and VOT the least. As expected, all interventions were less cost effective in unselected persons with LTBI. The highest incremental cost-effectiveness ratios were for VOT with estimated costs of $44,042 per DALY averted and $197,411 per TB case prevented.

Table 2: Projected costs of strategies using digital support for active TB treatment

Digital support strategy	Cost per person (95% UR), $	Incremental savings vs. DOT, $
Drug Susceptible TB Cohort		
Health system perspective		
DOT (comparator)	$930 ($876, $1 095)	
VOT	$567 ($529, $660)	$363 ($302, $490)
MM (Wisepill[@])	$423 ($392, $511)	$507 ($450, $ 631)
MM (99DOTS[@])	$394 ($363, $482)	$536 ($479, $660)
Societal perspective		
DOT (comparator)	$1 249 ($903, $3 069)	
VOT	$718 ($572, $1 170)	$531 ($69, $2 320)
MM (Wisepill[@])	$574 ($431, $1 032)	$675 ($217, $2 394)
MM (99DOTS[@])	$545 ($402, $1 003)	$704 ($249, $2 463)
MDR-TB Cohort		
Health system perspective		
DOT (comparator)	$12 585 ($12 395, $13 184)	
VOT	$11 177 ($11 027, $11 563)	$1 409 ($1 212, $1 826)
MM (Wisepill[@])	$10 754 ($10 623, $11 128)	$1 831 ($1 648, $2 235)
MM (99DOTS[@])	$10 715 ($10 584, $11 089)	$1 870 ($1 686, $2 274)
Societal perspective		
DOT (comparator)	$13 650 ($12 537, $19 923)	
VOT	$11 648 ($11 224, $12 769)	$2 002 ($371, $8 095)
MM (Wisepill[@])	$11 225 ($10 817, $12 358)	$2 425 ($789, $8 195)
MM (99DOTS[@])	$11 186 ($10 779, $12 319)	$2 463 ($828, $8 234)

Costs are expressed in 2016 US Dollars (USD).
UR, uncertainty range

Table 5: Projected cost effectiveness of strategies using digital support for LTBI treatment [a]

Digital support strategy	Cost per person (95% UR), $	Incr. cost vs. SAT, $	DALYs accrued (95% UR)	Incr. cost per DALY averted vs. SAT	TB Incidence (95% UR), %	Incr. cost per TB case prevented vs. SAT
LTBI Cohort- Close contacts						
Health system perspective						
SAT	$60 ($50, $103)	-	0.1 (0.07, 0.24)	-	2.0 (1.5, 4.6)	-
MM (Wisepill)	$96 ($84, $136)	$36 ($29, 38)	0.07 (0.05, 0.17)	$1 178 ($375, $2 171)	1.4 (1.1, 3.4)	$5 836 ($1 875, $10 704)
MM (99DOTS)	$67 ($55, $107)	$7 (-$7*, $8)	0.07 (0.05, 0.17)	$210 (-$10*, $445)	1.4 (1.1, 3.4)	$1 038 (-$40*, $2 195)
VOT	$356 ($314, $421)	$296 ($246, $340)	0.07 (0.05, 0.17)	$9 805 ($3 658, $17 596)	1.4 (1.1, 3.4)	$48 551 ($18 744, $83 722)
SMS	$65 ($53, $105)	$5 (-$6*, $8)	0.06 (0.03, 0.16)	$123 (-$57*, $311)	1.2 (0.8, 3.1)	$611 (-$273*, $1 556)
Societal perspective						
SAT	$181 ($79, $477)	-	0.1 (0.07, 0.24)	-	2.0 (1.5, 4.6)	-
MM (Wisepill)	$226 ($114, $546)	$45 ($24, $71)	0.07 (0.05, 0.17)	$1 495 ($389, $2 801)	1.4 (1.1, 3.4)	$7 404 ($1 816, $13 477)
MM (99DOTS)	$197 ($85, $517)	$16 (-$5, $42)	0.07 (0.05, 0.17)	$527 (-$100, $1 356)	1.4 (1.1, 3.4)	$2 608 (-$564*, $6 414)
VOT	$486 ($358, $806)	$305 ($250, $355)	0.07 (0.05, 0.17)	$10 122 ($3 730, $17 547)	1.4 (1.1, 3.4)	$50 119 ($18 756, $86 092)
SMS	$198 ($82, $531)	$17 (-$13*, $58)	0.06 (0.03, 0.16)	$440 (-$168*, $1 223)	1.2 (0.8, 3.1)	$2 180 (-$819*, $5 837)
LTBI Cohort- General population newly diagnosed with LTBI						
Health system perspective						
SAT	$50 ($39, $83)	-	0.030 (0.030, 0.055)	-	0.7 (0.6, 1.2)	-
MM (Wisepill)	$89 ($76, $124)	$39 ($37, $41)	0.023 (0.022, 0.044)	$5 520 ($2 722, $7 818)	0.5 (0.5, 1.0)	$24 745 ($12 327, $35 197)
MM (99DOTS)	$60 ($46, $94)	$10 ($8, $12)	0.023 (0.022, 0.044)	$1 370 ($639, $1 849)	0.5 (0.5, 1.0)	$6 180 ($2 893, $8 273)
VOT	$349 ($303, $412)	$299 ($251, $346)	0.023 (0.022, 0.044)	$42 481 ($20 534, $60 702)	0.5 (0.5, 1.0)	$190 415 ($92 588, $271 118)
SMS	$59 ($45, $95)	$9 ($7, $13)	0.021 (0.017, 0.042)	$1 000 ($383, $1 479)	0.5 (0.3, 0.9)	$4 483 ($1 755, $6 632)
Societal perspective						
SAT	$167 ($63, $445)	-	0.030 (0.030, 0.055)	-	0.7 (0.6, 1.2)	-
MM (Wisepill)	$216 ($101, $519)	$49 ($38, $76)	0.023 (0.022, 0.044)	$7 081 ($3 080, $10 460)	0.5 (0.5, 1.0)	$31 740 ($14 115, $45 303)
MM (99DOTS)	$187 ($72, $490)	$20 ($8, $47)	0.023 (0.022, 0.044)	$2 931 ($804, $5 508)	0.5 (0.5, 1.0)	$13 136 ($3 656, $24 628)
VOT	$477 ($342, $783)	$310 ($256, $362)	0.023 (0.022, 0.044)	$44 042 ($20 986, $62 452)	0.5 (0.5, 1.0)	$197 411 ($96 567, $278 873)
SMS	$190 ($72, $507)	$23 ($7, $68)	0.021 (0.017, 0.042)	$2 561 ($535, $5 166)	0.5 (0.3, 0.9)	$11 479 ($2 407, $22 869)

SAT, self-administered treatment. SMS, short message service. VOT, video-observed therapy. MM, medication monitor. Incr., incremental. UR, uncertainty range.
[a] Outcomes projected over a 20-year time horizon, with 3% discounting. All costs and incremental cost-effectiveness ratios in 2016 USD.
***Negative values indicate cost saving**

Scenario and sensitivity analyses

In the additional analysis for the active TB cohort, where MM and VOT were assumed to lead to better treatment outcomes than DOT, digital technologies were estimated to improve treatment success rates in the DS-TB cohort from 71% (95% UR: 71 – 72%) with DOT to 83% (95% UR: 79 - 87%), and to reduce DALYs accrued by 39%, from 3.2 (95% UR: 3.1 – 3.3) to 1.9 (95% UR: 1.6 – 2.4) per patient. With this scenario, societal cost savings relative to DOT were $543 with VOT, $687 with the Wisepill® MM, and $716 with the 99DOTS® MM. For the MDR-TB cohort, these technologies were projected to improve treatment success rates from 59% with standard DOT (95% UR: 57 – 62) to 75% (95% UR 69 – 80%), and reduce DALYs by 35%, from 5.2 (95% UR: 4.8 - 5.6) to 3.4 (95% UR: 2.9 – 4.2) per patient.

The additional scenario analysis for our LTBI model, which set effectiveness equal for all digital interventions so as to compare their costs, yielded results consistent with our primary findings. In this analysis, two-way SMS and 99DOTS® MM remained the most cost-effective interventions: the incremental cost of SMS was $164 (95% UR $29 saving – $362 cost) per DALY averted, and $814 ($137 saving – $1781 cost) per TB case prevented.

In the active TB cohorts, the probabilistic sensitivity analysis suggested that MM and VOT were likely to be cost saving within all model parameter ranges considered. For the LTBI models, SMS, 99DOTS® MM and Wisepill® MM were cost-effective (using $8,650, the mean per capita GDP in Brazil as the willingness to pay threshold) relative to SAT in 100% of simulations among close contacts of persons with LTBI. Among members of the general population newly diagnosed with LTBI, these technologies were cost-effective in more than 90% of simulations, using the same willingness-to-pay threshold. VOT was cost-effective in only 60% of simulations in the cohort of close contacts, and was not cost-effective among members of the general population with LTBI.

DISCUSSION

This analysis is the first to examine the potential cost and impact of digital technologies as applied under program conditions in a high TB-burden country. It provides preliminary insights into the potential impact and cost of several approaches to TB treatment support in this context. For active TB, we estimated substantial cost savings with VOT and MMs, including savings to patients and their families, compared to conventional in-person DOT. Compared to SAT for

LTBI treatment, two-way SMS and MMs are projected to be the most cost-effective technologies, especially for close contacts with LTBI; they are less cost-effective for others with LTBI. Until VOT becomes cheaper, it will likely be substantially less cost-effective for supporting LTBI treatment as currently delivered in Brazil and similar settings, despite improvements in rates of treatment completion. Although Brazil was the focus of our analysis, these results could potentially be relevant to other settings—recognizing that treatment practices will vary, e.g. in many settings, 6 months of isoniazid is the norm when LTBI is treated.

Our analysis highlights the paucity of published data on the clinical impact of digital interventions for TB. Few randomized trials exist, and many of the published results are from studies in very specific treatment settings e.g. for active TB treatment in New York and China, and HIV treatment in Kenya; these may not be generalizable to other populations and clinical settings including active and LTBI treatment in Brazil. Consequently, our analyses relied on estimates of clinical effectiveness that were often extrapolated from short-term data regarding adherence. Moreover, we based several estimates on the Chinese study of medication monitors where the control arm involved a mix of directly observed and self-administered therapy, which could overestimate the benefit of MM when compared with true DOT. We investigated the impact of uncertainty in our parameter estimates through extensive sensitivity analyses. However, if subsequent field trials suggest poorer clinical outcomes for a given digital support technology vs. conventional DOT, that technology is unlikely to be implemented further in active TB treatment, regardless of associated cost savings.

Published data on the costs of digital interventions are also scarce and sometimes out-dated. Particularly in low- and middle-income countries, technology-related costs can change rapidly due to improvements in infrastructure, such as internet connectivity. Whenever possible, we contacted study authors and manufacturers to obtain the best available cost estimates, and accounted for variability and uncertainty in sensitivity analyses. It should be noted that technology costs considered in this study do not include initial technology development and upstream support as they are beyond the scope of our analyses. There are also costs inherent to implementing technologies at large scale—beyond costs of training, hardware, and software—which are difficult to capture.

In our study, we assumed that costs and outcomes for standard care of active TB reflected direct observation. This assumption almost certainly overestimated the total number and cost of

DOT visits that in fact occur under program conditions. We did not have data for the precise number of DOT visits that actually take place. We may also have overestimated use of Xpert®MTB/RIF for TB diagnosis, which could lead to some overestimation of diagnostic costs for persons with LTBI who subsequently develop active TB. Furthermore, our models assumed 100% adoption of the digital technologies. Under program conditions, uptake is likely to be less – a point again explored via varying efficacy estimates in sensitivity analysis. Additional analyses involving variable uptake as well as combinations of these technologies, or only partial replacement of DOT in active TB, can provide further insight.

In Brazil, the estimated costs of TB for the health system and for patients and families are substantially lower than in a higher-income setting like the US. For example, Castro and colleagues estimated health system costs of $17,000 for each case of drug-susceptible TB, plus additional costs to patients and families of $3,000, and lost income of $374,000 for each patient who dies prematurely from drug-susceptible TB [44]. Hence to the extent that digital technologies reduce health system costs, and might potentially improve treatment outcomes in LTBI, resulting savings could be greater in higher-income settings. In the case of LTBI, where we assumed improved treatment adherence with the digital technologies, and hence a lower risk of future reactivation, we did not consider societal cost savings related to reductions in subsequent death and long-term disability. However, we did estimate DALYs averted.

In the future, digital support strategies may not only serve to improve adherence to TB and LTBI treatment, but may also improve monitoring of adverse events, a particular concern with SAT. SMS and VOT could allow patients to report potential adverse reactions and other concerns in a more timely manner, potentially improving outcomes and reducing costs. Our models could not account for this additional advantage, due to the lack of published evidence describing it. As additional trial data become available, this will be a worthwhile avenue of inquiry. More generally, digital technologies offer the possibility of detecting adherence gaps, in a less intrusive and expensive manner than traditional DOT. Any such gaps must then be addressed by tailored, patient-centered approaches which could include digital and/or in-person interactions.

As in other health domains, digital technologies can potentially replace or enhance existing treatment models [45, 46], but such a paradigm shift comes with challenges in development,

design, implementation, maintenance, accessibility and acceptability [47, 48]. For example, patients theoretically could “cheat” medication monitor systems by opening dispensers or blister packs without ingesting medication; this would falsely be recorded as good adherence [29, 34]. Although not completely foolproof, VOT maintains direct observation of medication ingestion, but may be perceived as intrusive by some patients [49]. When adopting digital technologies in the TB context, we can draw lessons from other fields where solutions were tailored to the perspectives of patients and providers to enhance feasibility [50, 51].

Digital support technologies may be more cost-effective with intermittent INH treatment, or with newer and shorter LTBI medication regimens, such as the 12-dose weekly INH/rifapentine combination. This was initially administered under direct, in-person observation [52]; however, a recent study reported no benefit for one-way SMS reminders added to standard SAT for this regimen [53]. Increasing global availability of these regimens justifies further evaluation of the cost-effectiveness of two-way SMS, MM, and VOT to support shorter-course LTBI treatment. It is also conceivable that with higher adherence to the self-administered shorter-course regimens, digital technologies could in fact provide less benefit in this regard; this possibility also warrants further evaluation.

CONCLUSION

Although DOT has long been held up as the paragon for active TB treatment support, it is not always possible to implement optimally. Our analysis shows that that digital technologies may reduce costs and improve treatment support for persons treated for active TB. However, more evidence of their value is needed, especially in the context of TB care. Furthermore, this analysis again emphasizes that LTBI treatment and treatment support should focus on persons at higher risk of developing active TB. By helping to improve the management of LTBI, digital technologies could contribute to reducing TB incidence and meeting the goals of the WHO’s End TB Strategy.

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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.

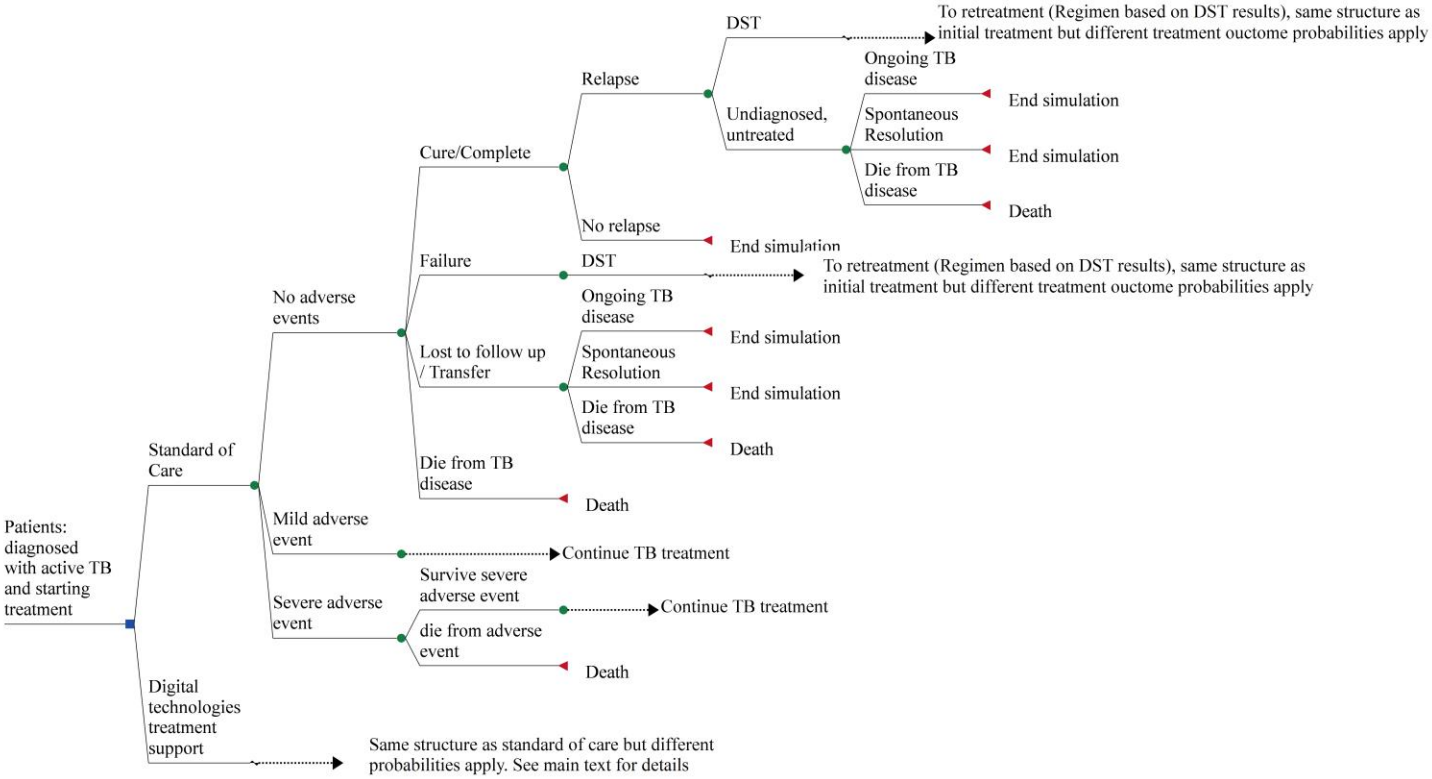
Drug-susceptible TB (DS-TB) cohort – For the DS-TB cohort, individuals were assumed to be newly diagnosed with TB, to have received no previous treatment, and to have had no contact with multidrug resistant TB (MDR-TB). Individuals were treated with a 6-month standard first-line treatment regimen. As 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 A2 [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 A1.

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 A1).

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 A1. 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 A1: 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 A1). 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 A1: 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)

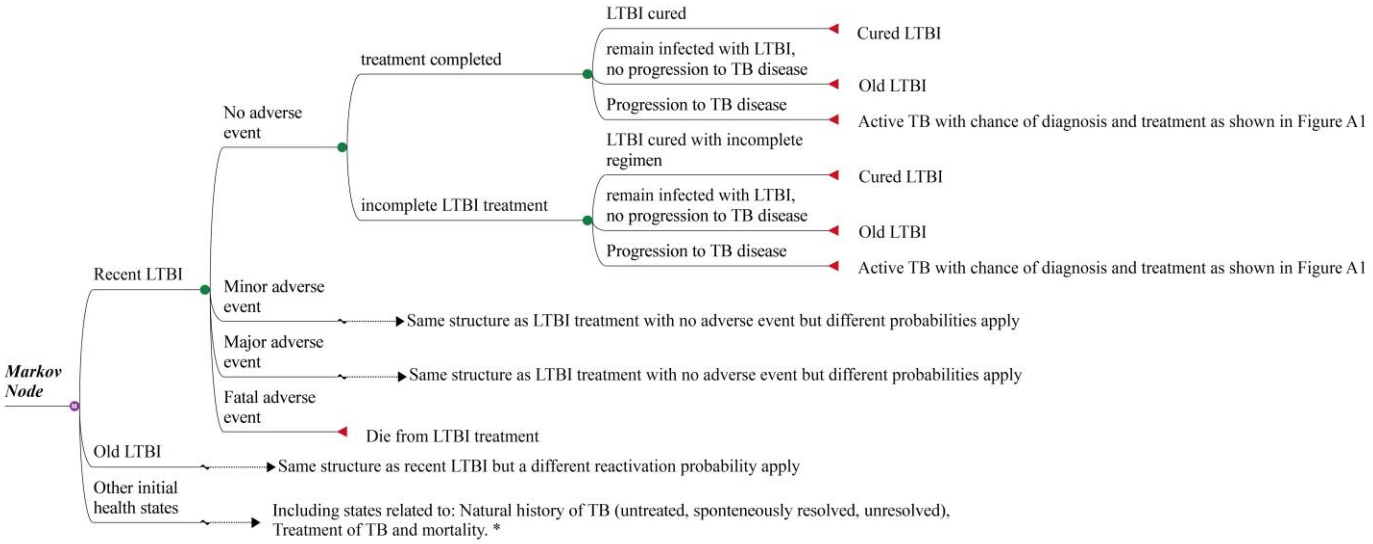
Table A2: Treatment regimens for DS-TB, MDR-TB, and LTBI

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 A2.

Figure A2: 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 A3a. 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 A3b: 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 A4-A9.

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 A4: 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 A5: 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 A6: 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 A4 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 A7: Per person health system costs for DS-TB and MDR-TB re-treatment, Brazilian standard of care

	Value	Ref.
Subtotal - for pre-diagnosis (Table A4 for DS-TB above) [h]	*$18.39*	*Table A4 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 A8) 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 A8: 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 A9)

Table A9a: 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 A9b: 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 A9c: Per person Technology costs for video-observed treatment intervention[u]

	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**		

[u] all other costs shown in Tables A4 and A6 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 A10). 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 A10: 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 first year	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 A3).

LTBI cohort

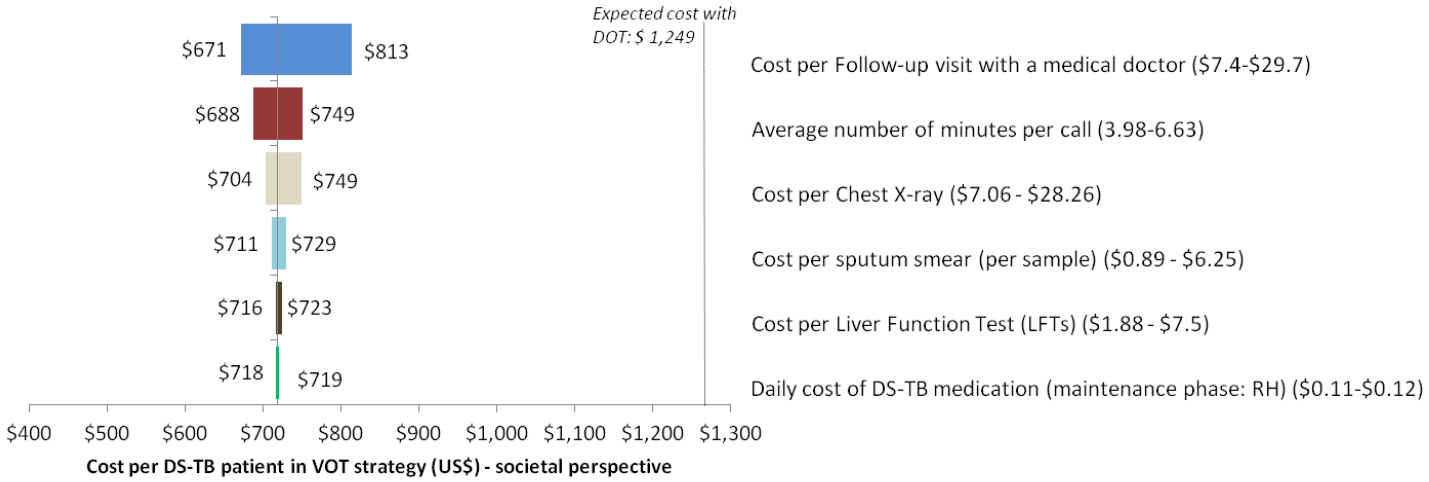
In univariate sensitivity analyses focusing on cost per TB case prevented, the probability of progressing from LTBI to active TB was the most influential model parameter for all digital strategies (Figure A4). Univariate sensitivity analyses focusing on cost per DALY averted indicated that the probability 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 A5).

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.

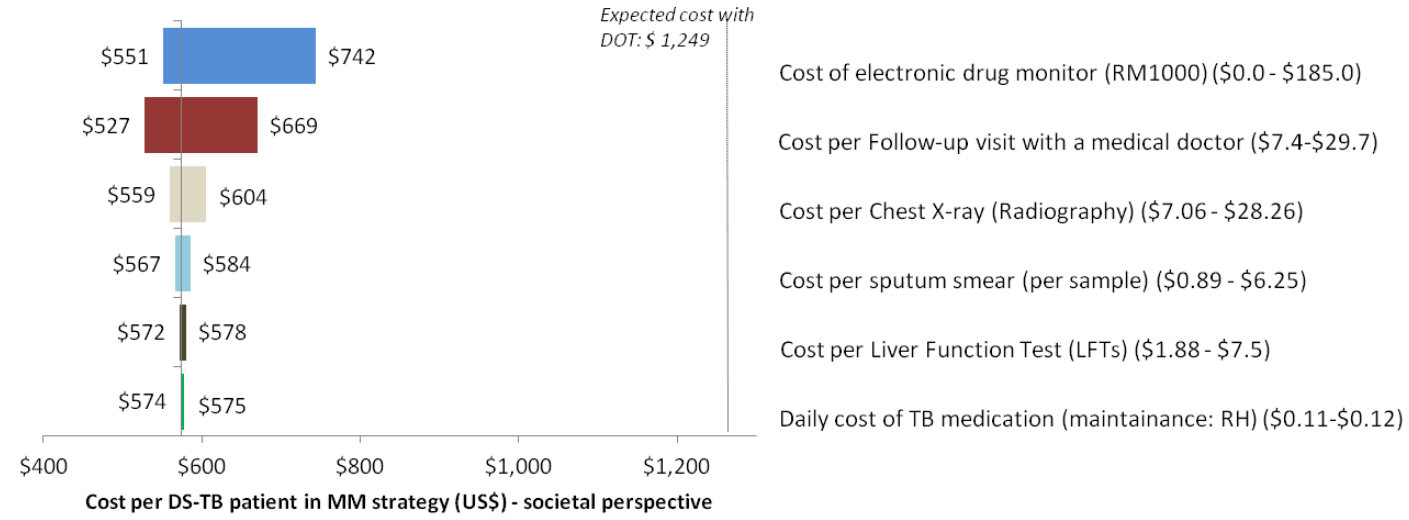
Cost-effectiveness acceptability curves, which represent the probability that the implementation of each digital intervention will be cost-effective relative to SAT as a function of the decision-makers' willingness-to-pay, are shown in Figure A6.

Figure A3: 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

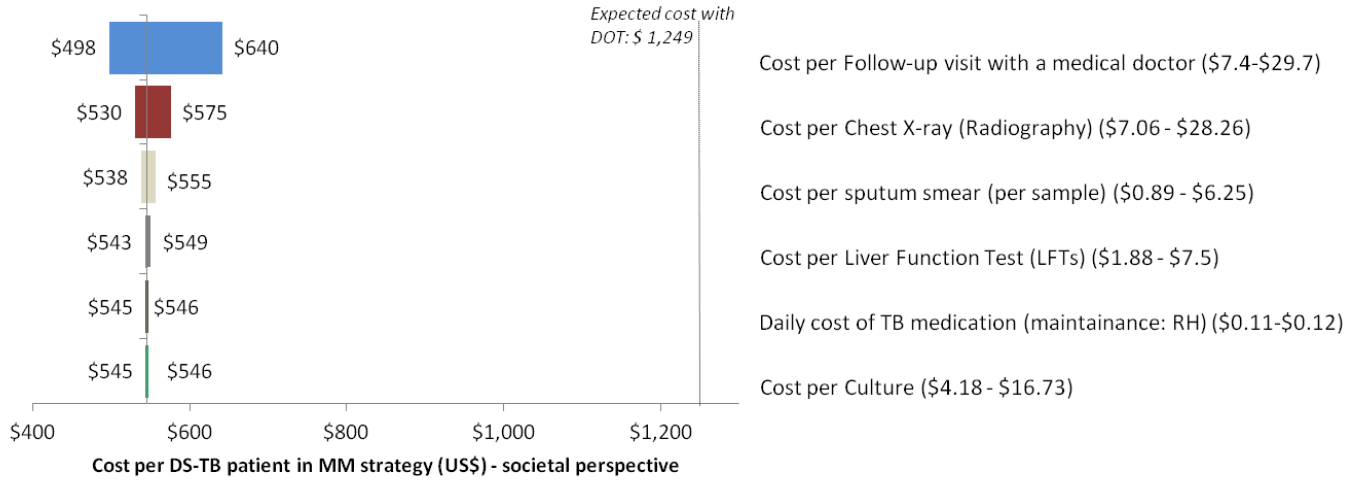
(i) VOT strategy for DS-TB



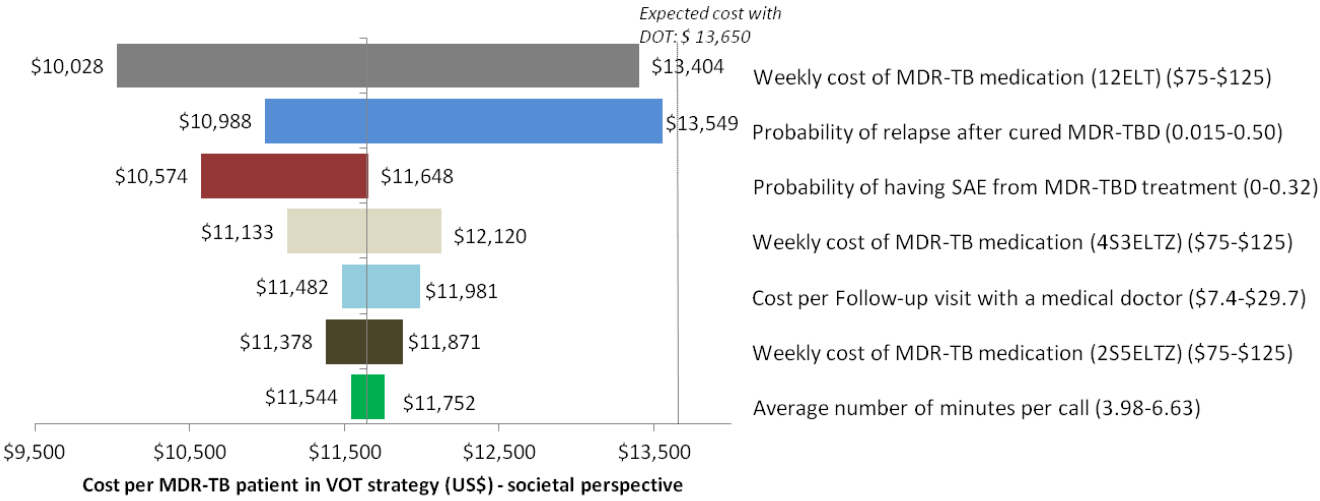
(ii) Wisepill medication monitor strategy for DS-TB



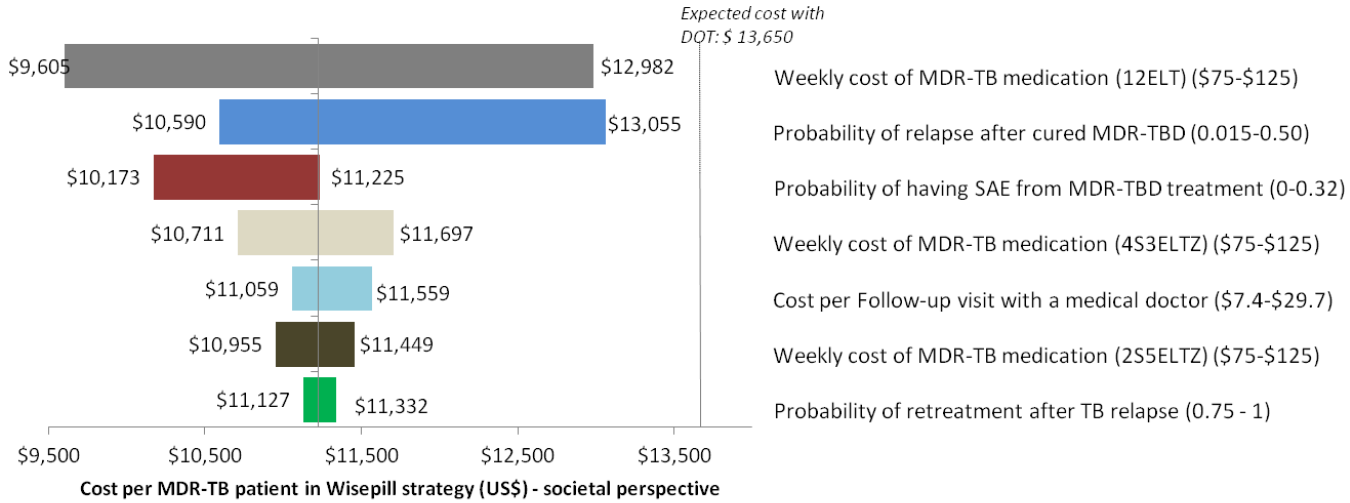
(iii) 99DOTS medication monitor strategy for DS-TB



(iv) VOT strategy for MDR-TB



(v) Wisepill medication monitor strategy for MDR-TB



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

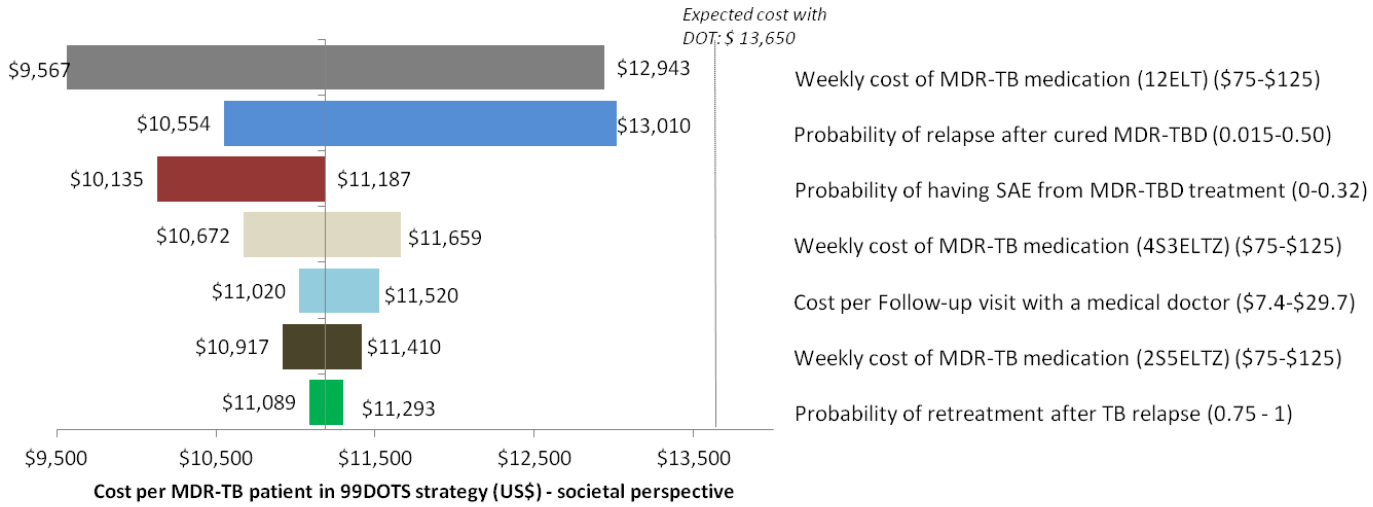
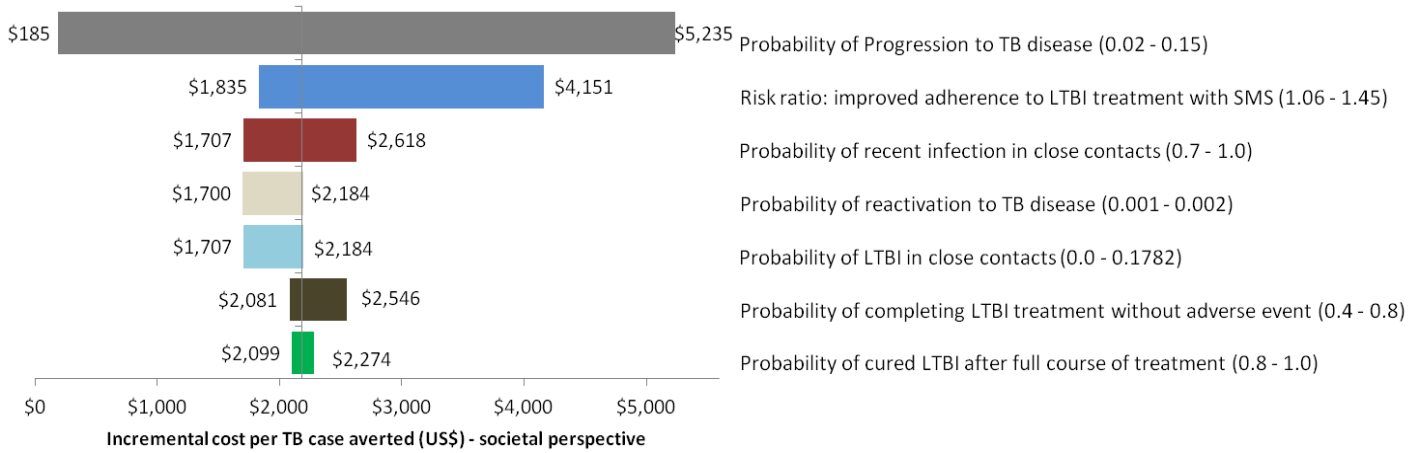
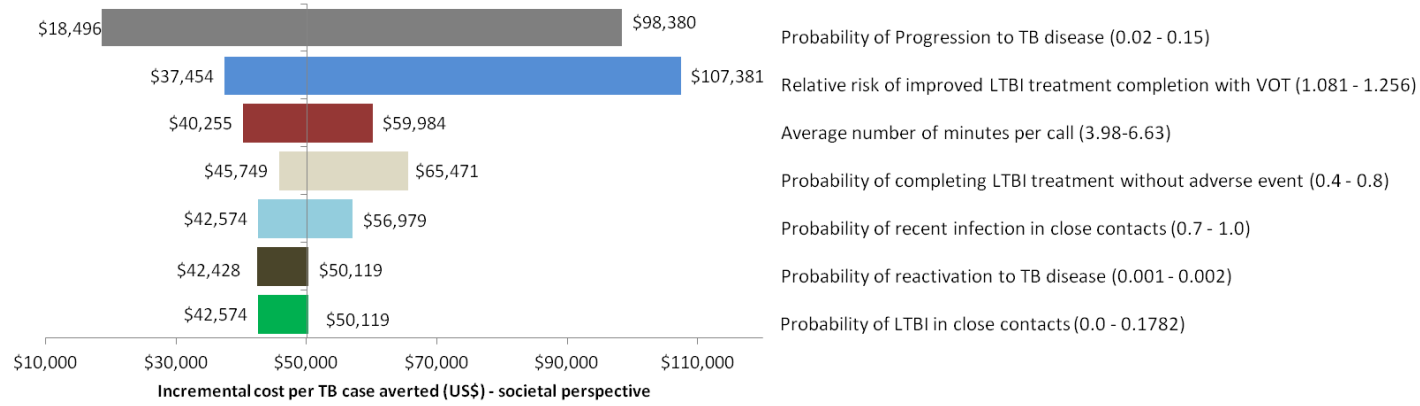


Figure A4: Tornado diagrams of the results of univariate sensitivity analyses with respect to TB cases averted, in the treatment of latent TB infection using (i) two-way SMS; (ii) video-observed therapy; (iii) Wisepill medication monitors; and (iv) 99DOTS medication monitors

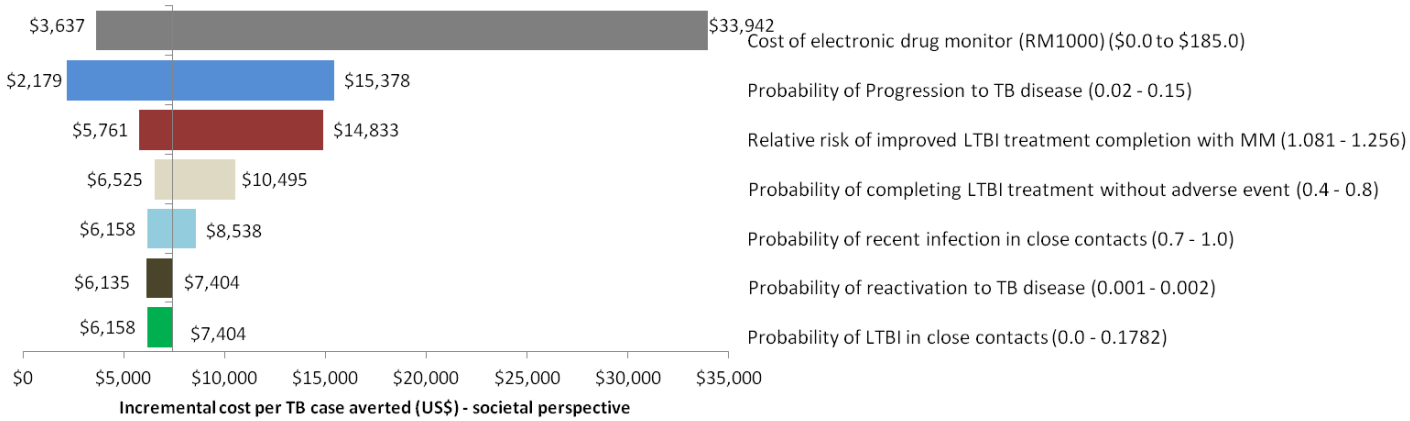
(i) SMS strategy



(ii) VOT strategy



(iii) Wisepill medication monitor strategy



(iv) 99DOTS medication monitor strategy

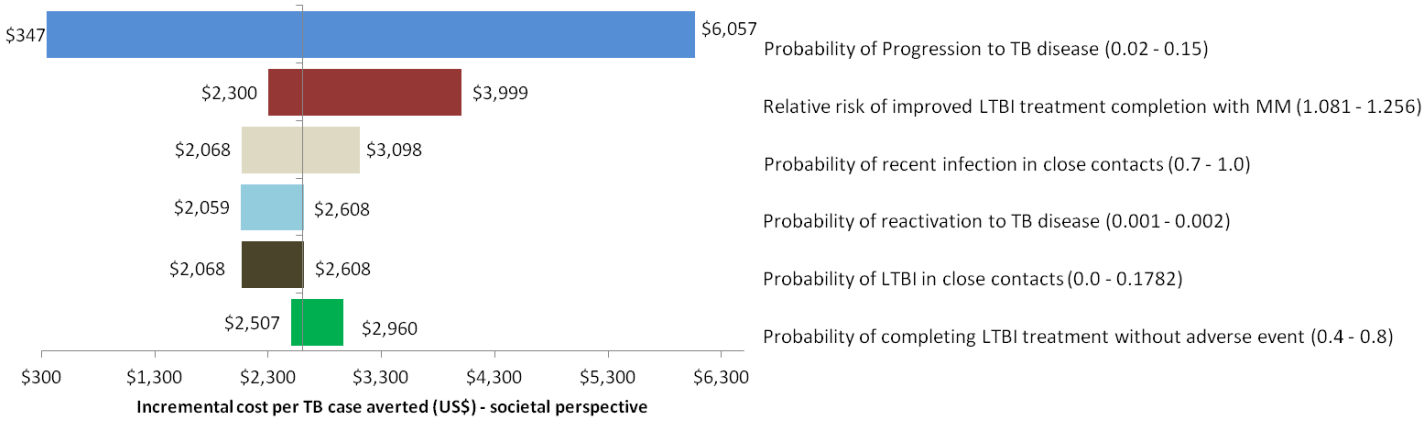
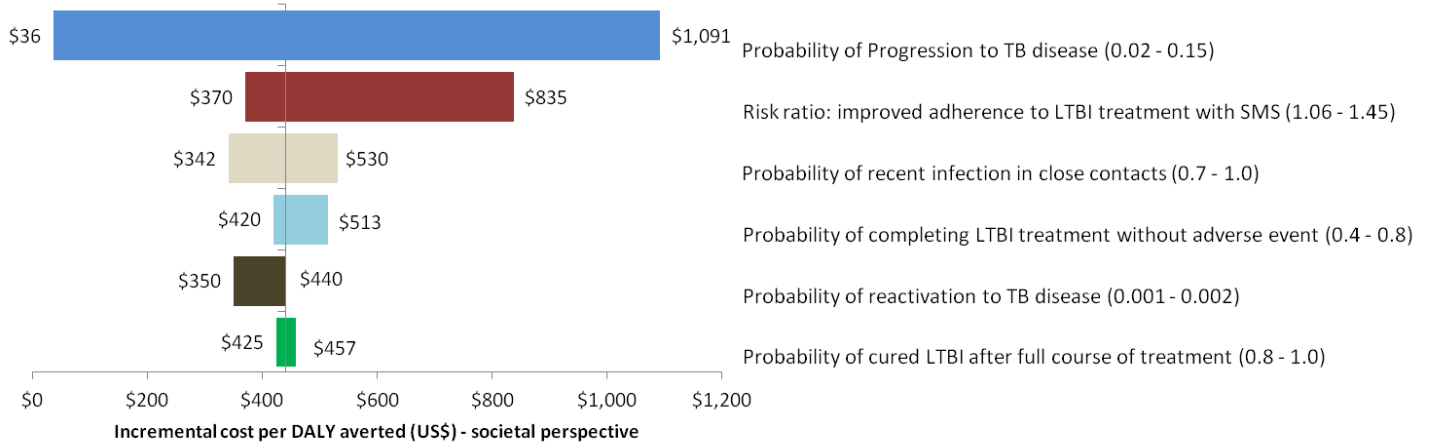
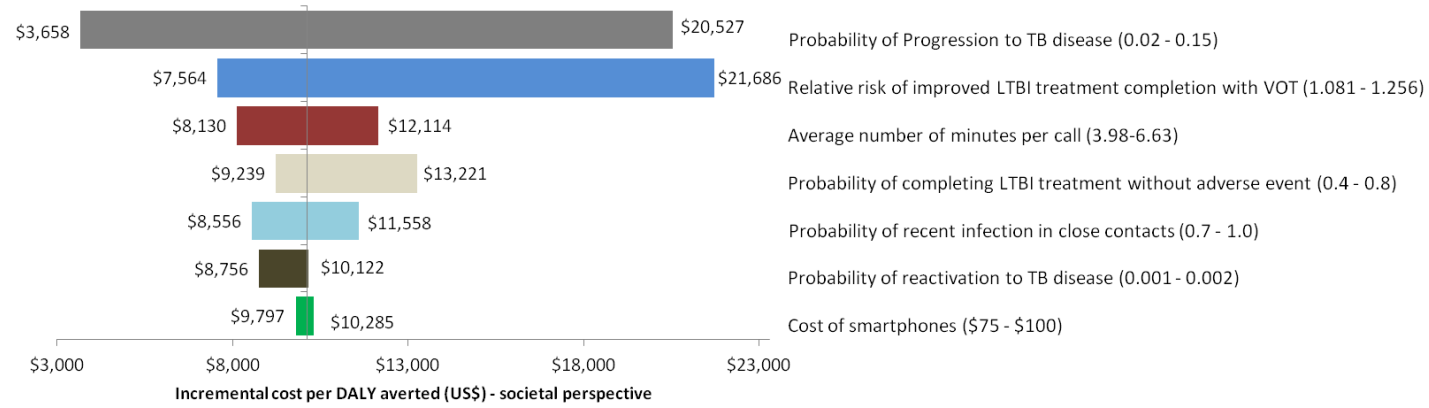


Figure A5: Tornado diagrams of the results of univariate sensitivity analyses with respect to DALYs averted, in the treatment of latent TB infection using (i) two-way SMS; (ii) video-observed therapy; (iii) Wisepill medication monitors; and (iv) 99DOTS medication monitors

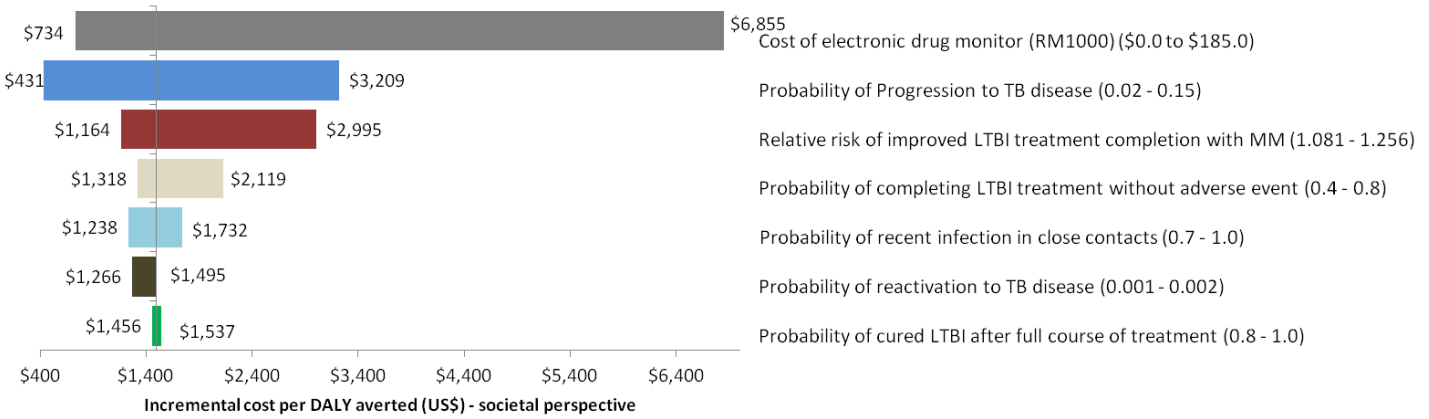
(i) SMS strategy



(ii) VOT strategy



(iii) Wisepill medication monitor strategy



(iv) 99DOTS medication monitor strategy

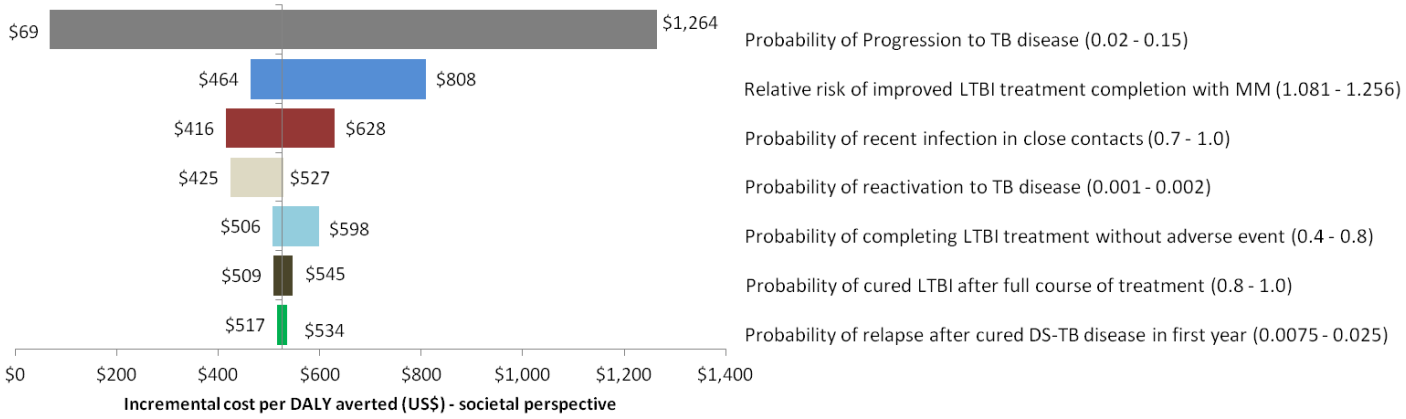
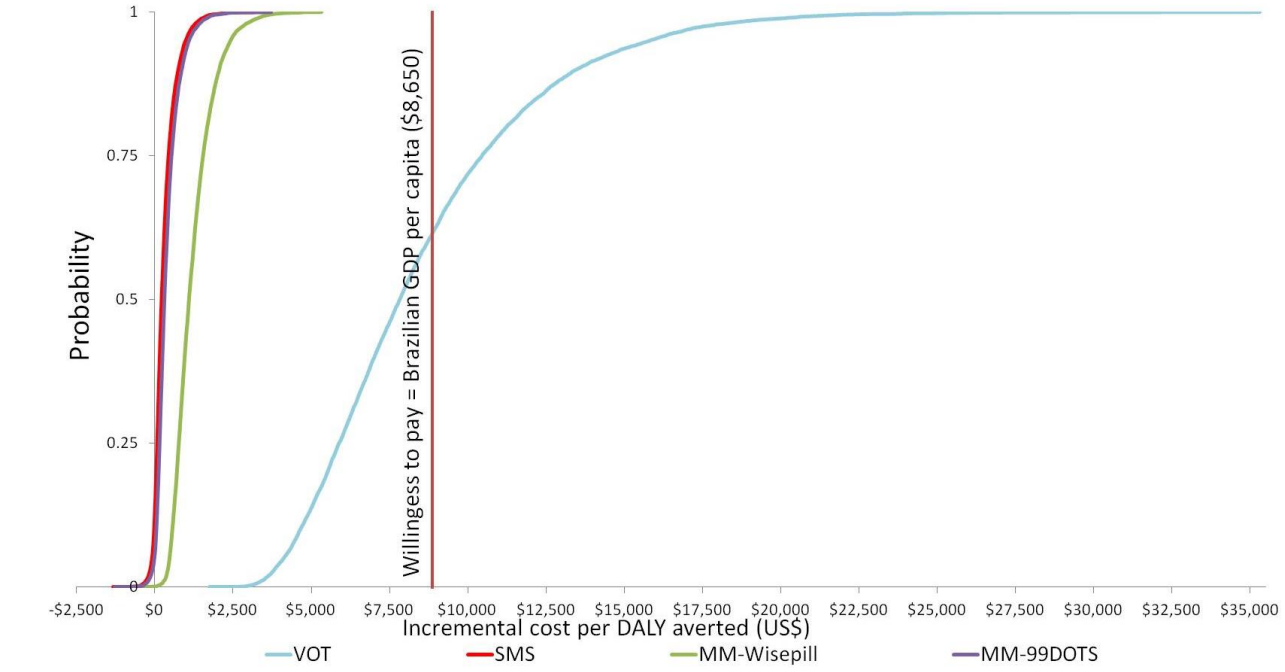
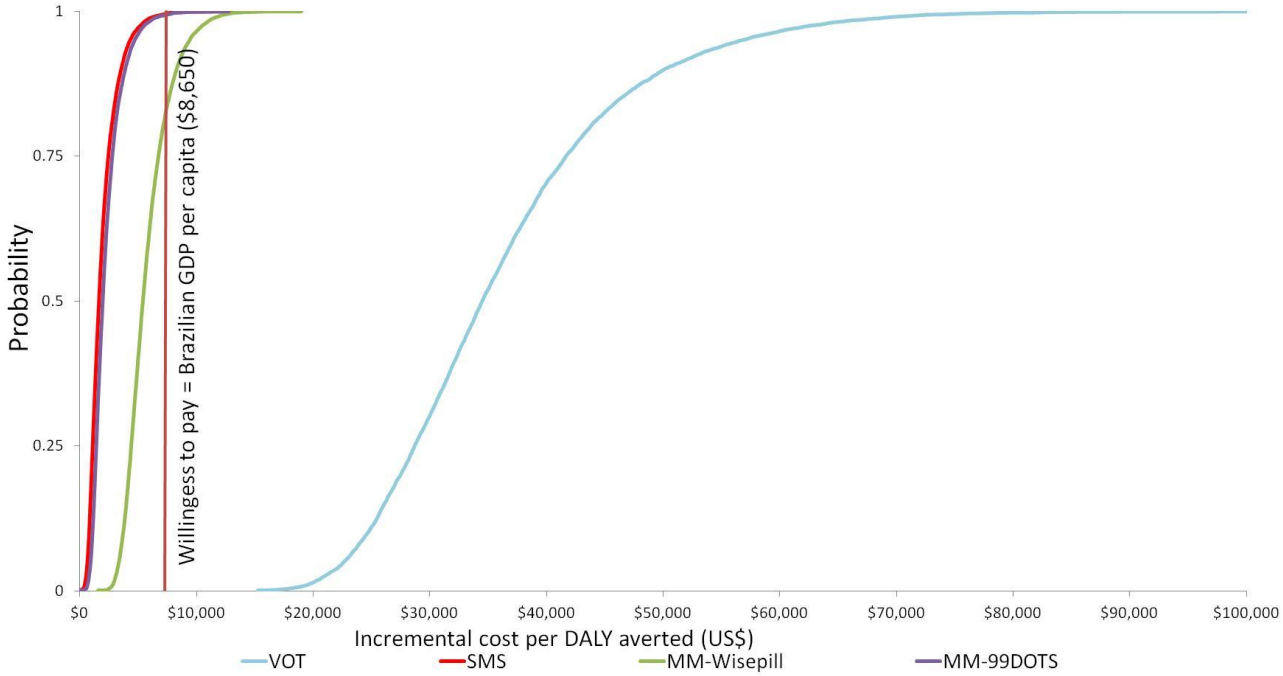


Figure A6. Cost-effectiveness acceptability curves comparing digital interventions to self-administered treatment, among (i) close contacts of persons with active TB having tested positive for LTBI and (ii) members of the general population having tested positive for LTBI



(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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